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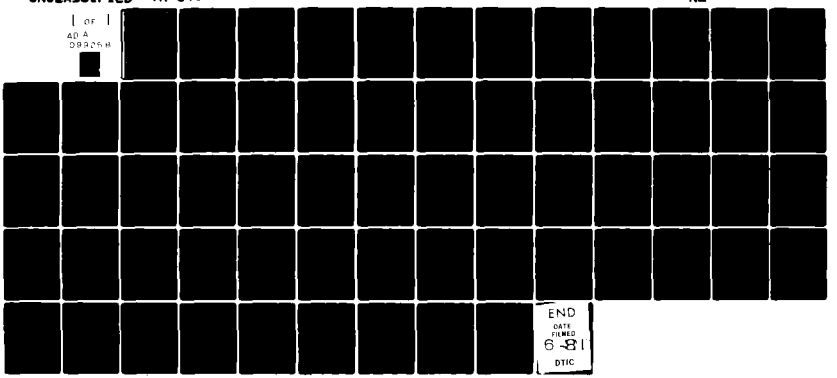

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REVIEWS OF PERTINENT LITERATURE IN SHOCK

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Oklahoma City, Oklahoma

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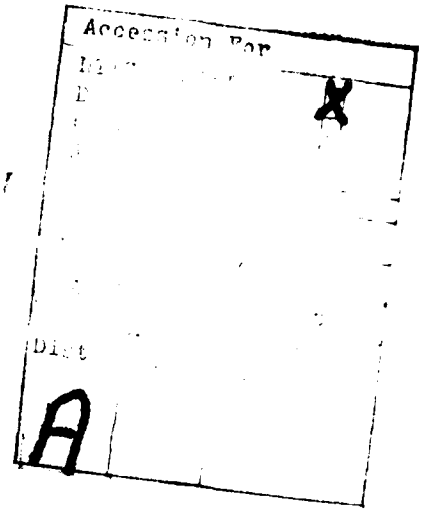

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(10) L. B. Hinshaw and P. R. Tomey

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ABSTRACT REFERENCE LIST

Volume 1 for 1981

1. ACTION OF HISTAMINE ON THE MESENTERIC MICROVASCULATURE. J Fox, F Galey, H Wayland. Microvascular Research 19:108-126 (1980)..... 1

2. COMPLEMENT-DEPENDENT ACTIVATION OF CANINE PLATELETS BY ENDOTOXIN AND COLLAGEN: *IN VITRO* STUDIES. TL Murphy, FB Taylor, III, IM Welsman, JM Gilliam, FB Taylor, Jr. Clinical Immunology and Immunopathology 16:57-71 (1980)..... 1

3. MECHANISMS OF IMPAIRED CARDIAC FUNCTION BY VASOPRESSIN. MF Wilson, DJ Brackett, LT Archer, LB Hinshaw. Ann. Surg. 191:494-500, No. 4, (1980)..... 2

4. RETICULOENDOTHELIAL CLEARANCE OF BLOOD-BORNE PARTICULATES: RELEVANCE TO EXPERIMENTAL LUNG MICROEMBOLIZATION AND VASCULAR INJURY. GD Niehaus, PR Schumacker, TM Saba. Ann. Surg. 191:479-487, No. 4, (1980)..... 2

5. GRADED INTESTINAL VASCULAR OBSTRUCTION: I. DESCRIPTION OF AN EXPERIMENTAL SHOCK MODEL IN THE RAT. E. Haglind, U Haglund, O Lundgren, M Romanus, T Scherstén. Circ. Shock 7:83-91 (1980).. 3

6. EFFECT OF HEMORRHAGIC SHOCK ON THE PERFORMANCE, O_2-CONSUMPTION AND ULTRASTRUCTURE OF ISOLATED RAT HEARTS. G Rubányi, AGB Kovách, E Koltay, T Nagy-Dóra, I Balogh, E Somogyi. Circ. Shock 7:59-70 (1980) 3

7. BLOCKADE OF OPIATE RECEPTORS WITH NALOXONE IMPROVES SURVIVAL AND CARDIAC PERFORMANCE IN CANINE ENDOTOXIC SHOCK. DG Reynolds, NJ Gurll, T Vargish, RB Lechner, AI Faden, JW Holaday. Circ. Shock 7:39-48 (1980)..... 3

8. NALOXONE REVERSAL OF HYPOVOLEMIC SHOCK IN DOGS. T Vargish, DG Reynolds, NJ Gurll, RB Lechner, JW Holaday, AI Faden. Circ. Shock 7:31-38 (1980) 4

9. REDUCED MYOCARDIAL RESPONSE TO CALCIUM DURING ENDOTOXIN SHOCK IN THE CAT. DJ McCaig, JR Parratt. Circ. Shock 7:23-30 (1980) ... 4

10. CONTINUOUS INTRAPERITONEAL ANTIBIOTIC LAVAGE IN THE MANAGEMENT OF PURULENT SEPSIS OF THE PELVIS. M Moukhtar and S Romney. Surg., Gynec., and Obstet. 150:548-550 (1980) 5

11. EFFECTS OF ENDOTOXIN ON BIOSYNTHESIS OF PROSTACYCLIN BY ISOLATED RABBIT PERITONEUM. H Bult, M Rampart, C Van Hove, AG Herman. Arch. int. Pharmacodyn. 242:288-290 (1979) 5

12. *IN VITRO* INFLUENCE OF ENDOTOXIN ON HUMAN MONONUCLEAR PHAGOCYTE STRUCTURE AND FUNCTION. 2. ENHANCEMENT OF THE EXPRESSION OF CYTOSTATIC AND CYTOLYTIC ACTIVITY OF NORMAL AND LYMPHOKINE-ACTIVATED MONOCYTES. J Hammerstrom. Acta. Path. Microbiol. Scand. Sec. C, 87:391-399 (1979) 5

13. *IN VITRO* INFLUENCE OF ENDOTOXIN ON HUMAN MONONUCLEAR PHAGOCYTE STRUCTURE AND FUNCTION. J Hammerstrom, G Unsgaard. Acta. Path. Microbiol. Scand. Sec. C, 87:381-389 (1979) 6

14. FUNDAMENTALS OF CLINICAL CARDIOLOGY. PREVENTION OF CARDIOGENIC SHOCK. JS Geddes, AAJ Adgey, JF Pantridge. American Heart Journal 99:243-254, No 2, (1980) 6

15. ENDOTOXEMIA OF CIRRHOSIS: AN OBSERVATION NOT SUBSTANTIATED. JT Fulenwider, C Sibley, SF Stein, B Evatt, BM Nordlinger, GL Ivey. Gastroenterology 78:1001-1004 (1980) 6

16. THE ROLE OF PROSTAGLANDINS IN ENDOTOXEMIA: COMPARISONS IN RESPONSE IN THE NONPREGNANT, MATERNAL, AND FETAL MODELS. I. PROSTAGLANDINS AND THE PULMONARY EFFECT OF EXPERIMENTAL ENDOTOXEMIA. RC Cefalo, PE Lewis, WF O'Brien, JR Fletcher, PW Ramwell. Am. J. of Ob. and Gyn. 137(1):53-57..... 7

17. IMPROVED PROGNOSIS FOR GRANULOCYTOPENIC PATIENTS WITH GRAM-NEGATIVE BACTEREMIA. LJ Love, SC Schimpff, CA Schiffer, PH Wiernik. The Am. J. of Med. 68(5):643-648..... 7

18. HYPOGLYCEMIA AS A MANIFESTATION OF SEPSIS. SI Miller, RJ Wallace, Jr., DM Musher, EJ Septimus, S Kohl, RE Baughn. The Am. J. of Med. 68(5):649-654..... 7

19. PROTECTION FROM OXYGEN TOXICITY WITH ENDOTOXIN. ROLE OF THE ENDOGENOUS ANTIOXIDANT ENZYMES OF THE LUNG. LFJ Summerville, D Massaro. J. Clin. Invest. 65:1104-1110 (1980) 8

20. PRETREATMENT WITH METHYLPREDNISOLONE SHORTENS SURVIVAL IN A CANINE MODEL OF PSEUDOMONAS PNEUMONIA. JD Katz, PG Barash, MD Tilson, W Gersoff, AR Guinazu, AE Baue. J. of Surg. Res. 28:260-268 (1980) 8

21. LUNG LYSOSOMAL ENZYME RELEASE DURING HEMORRHAGIC SHOCK AND ENDOTOXEMIA. RH Demling, R Proctor, N Duy, JR Starling. J. of Surg. Res. 28(3):269-279 (1980)..... 9

22. LUNG FLUID AND PROTEIN DYNAMICS DURING HEMORRHAGIC SHOCK, RESUSCITATION, AND RECOVERY. RH Demling. Circ. Shock 7:149-161 (1980). 9

23. MARROW CULTURE IN DIFFUSION CHAMGERS IN RABBITS: III. EFFECT OF ENDOTOXIN AND LEUKOCYTE PRODUCTS ON CELL PRODUCTION. R Willemze, RI Walker, JC Herion, JG Palmer. Am. J. of Hemat. 7:33-43 (1979) 10

24. HEMATOLOGIC RESPONSES INDUCED BY ENDOTOXIN IN NORMAL AND ENDOTOXIN-TOLERANT DOGS. TJ MacVittie, RI Walker. Exp. Hemat. 8:599-609, No 5, (1980) 10

25. RENAL EFFECTS OF DOPAMINE DURING PROLONGED HEMORRHAGIC HYPOTENSION IN THE DOG. RE Neiberger, JI Levin, JC Passmore. Circ. Shock 7:129-138 (1980). 11

26. MONITORING HEPATIC DYSFUNCITON DURING INTRAVENOUS HYPERALIMENTATION. BJ Rowlands, BV MacFadyen, P DeJong, SJ Dudrick. J. Surg. Res. 28:471-478 (1980) 11

27. RESPONSE OF THE PULMONARY MICROCIRCULATION TO FLUID LOADING AFTER HEMORRHAGIC SHOCK AND RESUSCITATION. RH Demling, M Manohar, JA Will. Surg. 87(5):552-559 (1980). 11

28. DIAGNOSIS AND TREATMENT OF CANNULA-RELATED INTRAVENOUS SEPSIS IN BURN PATIENTS. BA Pruitt, WF McManus, SH Kim, RC Treat. Ann. Surg. 191(5):546-553 (1980) 12

29. LIBERATION OF ENDOTOXIN FROM *ESCHERICHIA COLI* BY ADDITION OF ANTIBIOTICS. H Goto, S Nakamura. Japan. J. Exp. Med. 50:35-53, No 1 (1980). 12

30. BLOOD LEVELS OF 6 OXO-PROSTAGLANDIN $F_{1\alpha}$ DURING ENDOTOXIN-INDUCED HYPOTENSION IN RABBITS. H Bult, J Beetens, AG Herman. Europ. J. Pharmacol. 63:47-56 (1980) 13

31. ENDOTOXIN-ENHANCED SECRETION OF MACROPHAGE INSULIN-LIKE ACTIVITY. JP Filkins. J. Reticuloendothelia Soc. 27:507-511, No 5 (1980) . 13

32. *IN VITRO* PHAGOCYTOSIS BY *LIMULUS* BLOOD CELLS. PB Armstrong, J Levin. J. Invertebrate Pathol. 34:145-151 (1979). 14

33. SEPTIC SHOCK. LE Galin, I Dawidson, U Haglund, M Heideman, H Myrvold. Surg. Clin. N. Am. 60:161-174, No 1 (1980). 14

34. PULMONARY EDEMA-HYPOXIA AND OVERPERFUSION. NC Staub. N. Eng. J. Med. 302:1085-1087, No 19 (1980). 14

35. ENDOGENOUS PYROGEN RELEASE BY FETAL SHEEP AND PREGNANT SHEEP BLOOD LEUKOCYTES. NW Kasting, WL Veale, KE Cooper. Can J. Physiol. Pharmacol. 57:1453-1456 (1979) 15

36. GENETIC CONTROL OF PERIPHERAL LEUKOCYTE RESPONSE TO ENDOTOXIN IN MICE. MW Verghese, M Prince, R Snyderman. J. Immunol. 124: 2468-2473 (1980). 15

37. PATHOPHYSIOLOGY OF *CANDIDA ALBICANS* MENINGITIS IN NORMAL, NEUTROPENIC, AND GRANULOCYTE TRANSFUSED DOGS. HS Chow, SC Sarpel, RB Epstein. Blood 55:546-551 (1980). 15

38. CONTROL OF ARTERIAL PRESSURE AND RENAL FUNCTION DURING GLUCOCORTICOID EXCESS IN DOGS. JE Hall, CL Morse, MJ Smith, DB Young, AC Guyton. Hypertension 2:139-148 (1980) 16

39 THE INTERACTION OF LEUKOCYTES AND ERYTHROCYTES IN CAPILLARY AND POSTCAPILLARY VESSELS. GW Schmid-Schönbein, S Usami, R Skalak, S Chien. Microvasc. Res. 19:45-70 (1980) 16

40. ANOTHER LOOK AT SHOCK. WB Cannon. Path Res. Pract. 165:197-199 (1979). 17

41. PLASMA CATHECHOLAMINE LEVELS AND PULMONARY DYSFUNCTION IN SEPSIS. JK Bocking, WJ Sibbald, RL Holliday, S Scoot, T Viidik. Surg. Gynecol. & Obstet. 148:715-719 (1979) 18

42. DOCUMENTATION OF PULMONARY CAPILLARY PERMEABILITY IN THE ADULT RESPIRATORY DISTRESS SYNDROME ACCOMPANYING HUMAN SEPSIS. RR Anderson, RL Holliday, AA Driedger, M Lefcoe, B Reid, WJ Sibbald. Am. Rev. Resp. Dis 119:869-877 (1979) 18

43. ENHANCEMENT OF LEUKOCYTE ACTIVITY AGAINST *ESCHERICHIA COLI* AFTER BRIEF EXPOSURE TO CHLORAMPHENICOL. H Pruul, P McDonald. Antimicrobial Agnets and Chemotherapy. 16:695-700 (1979) 18

44. ENDOTOXIN-INDUCED CHANGES IN THE RABBIT'S BLOOD PICTURE. Z Konickova, Z Likovsky, L Pavkova. Physiol. Bohemoslov. 29:81-87 (1980) 19

45. THE RELATIONSHIP OF GLUCAGON AND INSULIN TO SEQUENTIAL CHANGES IN METABOLIC FUEL UTILIZATION IN SHOCK. CD Wood, Y Bentz, M Martin, WO Read. J Surg. Res. 28:239-245 (1980). 19

46. WEDGE BALLON CATHETER ANGIOGRAPHY IN THE CRITICAL CARE UNIT. MS Lefcoe, WJ Sibbald, RL Holliday. Critical Care Medicine 7:449-453 (1979). 19

47. GLUCOCORTICOID BINDING TO NORMAL AND ACTIVATED ALVEOLAR LUNG CELLS. SC George, TW Gudewicz, RC Jaffe. Lung 157:57-64 (1980). 20

48. BENEFICIAL ACTIONS OF IMIDAZOLE IN ENDOTOXIN SHOCK. EF Smith, III, JH Tabas, AM Lefer. Prostaglandins and Medicine 4:215-222 (1980) 20

49. THE EFFECT OF ENDOTOXIN SHOCK ON HISTAMINE AND HISTIDINE DECARBOXYLASE ENZYME ACTIVITIES IN VARIOUS TISSUES OF CATS. S Saleh, NG Waton, JR Parratt. Proc. B.P.S. 17-19 December, 1979 21

50. GRAM-NEGATIVE SEPSIS IN NEONATES: A NURSERY OUTBREAK DUE TO HAND CARRIAGE OF *CITROBACTER DIVERSUS*. MF Parry, JH Hutchinson, NA Brown, Chii-Huei Wu and L Estreller. Pediatrics 65:1105-1109, No 6, (1980) 21

51. PATHOPHYSIOLOGY OF SHOCK. H Haljam ä e, B Amundson, U Bagge, E Jennische, P-I Brånemark. Path Res. Pract. 165 200-211 (1979) . 22

52. BLOOD COAGULATION AND SHOCK. T Saldeen. Path. Res. Pract. 165:221-252 (1979) 22

53. MORPHOLOGIC DEVELOPMENT OF HUMAN SHOCK LUNG. UN Reide, CH Mittermayer, H Friedburg, K Wybitul, W Sandritter. Path. Res. Pract. 165:269-286 (1979) 22

54. EXPERIMENTAL STUDIES ON COAGULATION-FIBRINOLYTIC ACTIVITY OF WHITE BLOOD CELLS INFLUENCED BY ENDOTOXIN. N Sakuragawa, K Takahashi, M Yoshiyama, C Jimbo, K Niiya, M Matsuoka, Y Ohnishi. Thromb. Res. 8:887-891 (1976). 23

55. AGE-RELATED DIFFERENCES IN THERMOREGULATORY RESPONSES TO ENDOTOXIN IN RABBITS. M Székely, Z Szélenyi. Acta. Physiol. Acad. Scient. Hung. 54:389-399 (1979). 23

56. REACTIVITY OF THE CEREBROCORTICAL VASCULATURE AND ENERGY METABOLISM TO DIRECT CORTICAL STIMULATION IN HEMORRHAGIC SHOCK. E Dóra, AGB Kovach. Acta. Physiol. Acad. Scient. Hung. 54:347-361 (1979) 23

57. INTRACELLULAR OXYGEN TENSION AND ENERGY METABOLISM IN THE CAT BRAIN CORTEX DURING HAEMORRHAGIC SHOCK. AGB Kovach, E Dóra. Acta Physiol. Acad. Scient. Hung. 54(4):333-346 (1979). . 24

58. MYOCARDIAL RELAXATION. II. HEMODYNAMIC DETERMINANTS OF RATE OF LEFT VENTRICULAR ISOVOLUMIC PRESSURE DECLINE. WH Gaasch, AS Blaustein, CW Andrias, RP Donohue, B Avitall. Am. J. Physiol. 239 (Heart Circ. Physiol. 8):H1-H6 (1980). 24

59. RESPONSE OF SYSTEMIC ARTERIAL INPUT IMPEDANCE TO VOLUME EXPANSION AND HEMORRHAGE. JP Dujardin, DN Stone, LT Paul, HP Pieper. Am J. Physiol. 238(6):H902-H908 (1980) 25

60. EFFECT OF *SHIGELLA FLEXNERI* ENDOTOXIN ON UREAGENESIS AND LIVER ULTRASTRUCTURE IN RABBITS. M Yoshino. Exper. Mol. Pathol. 32: 253-263 (1980) 25

61. THE DYNAMICS OF THE LUNG FLUID FILTRATION SYSTEM IN DOGS WITH EDEMA. MH Gee, JA Spath. Circ. Res. 46(6):796-801 (1980) 26

62. LUNG TISSUE VOLUME DURING DEVELOPMENT OF EDEMA IN ISOLATED CANINE LUNGS. CR Felton, WG Johanson, Jr. J. Appl. Physiol: Respirat: Environ. Exercise Physiol. 48(6):1038-1044 (1980). . . 26

63. LIMITATIONS OF LACTATE PRODUCTION AS AN INDEX OF MYOCARDIAL ISCHEMIA. CS Apstein, F Gravino, WB Hood, Jr. Circ. 60: 877-888, No 4 (1979) 27

64. CHANGES IN SERUM LIPID ENDOTOXIN-POISONED MICE. S Sakaguchi, O Sakaguchi. Microbiol. Immunol. 24(4):357-360 (1980) 27

65. EFFECT OF *CORONARY SINUS OCCLUSION* ON CORONARY PRESSURE-FLOW RELATIONS. RF Bellamy, HS Lowensoh, W Ehrlich, RW Baer. Am. J. Physiol. 239 (Heart Circ. Physiol. 8):H57-H64 (1980). . . . 27

66. THE INTERRELATIONSHIP BETWEEN THROMBOXANE BIOSYNTHESIS, AGGREGATION AND 5-HYDROXYTRYPTAMINE SECRETION IN HUMAN PLATELETS *IN VITRO*. LC Best, TK Holland, PBB Jones, RGG Russell. Thromb. Haem. 43(1):38-40 (1979) 28

67. THE PROSTANOIDS IN HEMOSTASIS AND THROMBOSIS. JB Smith. Am. J. Path. 99:743-804, No 3 (1980) 28

68. MICROVASCULAR ARCHITECTURE OF ANTHROPOID PRIMATE INTESTINE. KG Swan, EK Spees, DG Reynolds, JC Kerr, MJ Zinner. Circ. Shock 5:374-382 (1978) 29

69. MORPHOLOGIC DEVELOPMENT OF HUMAN SHOCK LUNG. UN Riede, CH Mittermayer, H Friedburg, K Wybitul, W Sandritter. Path. Res. Pract. 165:269-286 (1979) 29

70. HEMODILUTION, OXYGEN CONSUMPTION, AND RECOVERY FROM SHOCK. I Dawidson. 1:7-86 (1980). 29

71. THE FUNCTIONING OF BLOOD PLATELETS. MB Zucker. Sci. Am. 242(6):86-102 (1980) 30

72. COMPLEMENT-INDUCED GRANULOCYTE AGGREGATION. AN UNSUSPECTED MECHANISM OF DISEASE. HS Jacob, PR Craddock, DE Hammerschmidt, CF Moldow. Seminars in Medicine of the Beth Israel Hospital Boston 302, 14:789-794 (1980). 30

73. GRANULOCYTE AGGREGATIN AS A MANIFESTATION OF MEMBRANE INTERACTIONS WITH COMPLEMENT: POSSIBLE ROLE IN LEUKOCYTE MARGINATION, MICROVASCULAR OCCLUSION, AND ENDOTHELIAL DAMAGE. PR Craddock, DE Hammerschmidt, CF Moldow, O Yamada, HS Jacob. Seminars in Hematology 16(2):140-147 (1979). 30

74. ASSOCIATION OF COMPLEMENT ACTIVATION AND ELEVATED PLASMA-C5A WITH ADULT RESPIRATORY DISTRESS SYNDROME. PATHOPHYSIOLOGICAL RELEVANCE AND POSSIBLE PROGNOSTIC VALUE. DE Hammerschmidt, LJ Weaver, LD Hudson, PR Craddock, HS Jacob. The Lancet 947-949 (1980) 30

75. AMINOGLYCOSIDE NEPHROTOXICITY: COMPARATIVE ASSESSMENT IN CRITICALLY ILL PATIENTS. ME Plaut, JJ Schentag, WJ Jusko. J. Med. 10(4): 256-267 (1979) 31

76. COMPARATIVE LOW-DOSE NEPHROTOXICITIES OF GENTAMICIN, TOBRAMICIN, AND AMIKACIN. GH Hottendorf, LL Gordon. Antimicrob. Agents and Chemother. 18(1):176-181 (1980). 32

77. EFFECT OF SEPSIS ON TISSUE ADENINE NUCLEOTIDE LEVELS. IH Chaudry, KA Wichterman, AE Baue. Surg. 85:205-11 (1979) 32

78. AMINO ACID METABOLISM IN DOGS WITH *E. COLI* BACTEREMIC SHOCK. LT Woolf, AC Groves, JH Duff. Surg. 85:212-218 (1979) 32

79. *E. COLI* ENDOTOXIN SHOCK IN THE BABOON: TREATMENT WITH LIDOCAINE OR INDOMETHACIN. JR Fletcher, PW Ramwell. Adv. in Prostagland. and Thrmboxane Res. 3:183 192 (1978) 33

80. INDOMETHACIN IMPROVES SURVIVAL AFTER ENDOTOXIN IN BABOONS. JR Fletcher, PW Ramwell. Adv. In Prostagland. and Thromboxane Res. 7:821-828 (1980) 33

81. THE PATHOPHYSIOLOGY OF SHOCK. RF Wilson. Intens. Care Med. 6:89-100 (1980). 33

82. THE SYSTEMIC SEPTIC RESPONSE: DOES THE ORGANISM MATTER? JB Wiles, FB Cerra, JH Siegel, JR Border. Crit. Care Med. 8(2): 55-60 (1980) 34

83. NETILMICIN: A REVIEW OF TOXICITY IN LABORATORY ANIMALS. FC Luft. J. Int. Med. Res. 6(4):286-299 (1978). 34

84. GENTAMICIN: TOXICITY IN PERSPECTIVE. WL Hewitt. Postgraduate Med. J. 50:55-59 (1974). 34

85. COMPARATIVE TOXICITY OF NETILMICIN AND GENTAMICIN IN SQUIRREL MONKEYS (*SAIMIRI SCIUREUS*). M Igarashi, JK Levy, J Jerger. J. Infet. Dis. 137(4):476-480 (1978) 35

86. NATURAL HISTORY OF AMINOGLYCOSIDE HEPHROTOXCITY IN THE DOG. RE Cronin, RE Bulger, P Southern, WL Henrich. J. Lab. Clin. Med. 95(3):463-474 (1980) 35

87. NEPHROTOXICITY OF GENTAMICIN AND TOBRAMYCIN GIVEN ONCE DAILY OR CONTINUOUSLY IN DOGS. N Reimer, D Bloxham, W Thompson. Antimicrob. Chemother. 4:85-101 (1978) 36

88. COMPARATIVE NEPHROTOXICITY OF AMINOGLYCOSIDE ANTIBIOTICS IN RATS. F Luft, R Block, R Sloan, M Yum, R Costello, D Maxwell. Infect. Dis. 138:541-545, No 4 (1978). 36

89. COMPARATIVE NEPHROTOXICITY OF GENTAMICIN AND TOBRAMYCIN IN RATS. D. Gilbert, C Plamp, P Starr, W Bennett, D Houghton, G Porter. Antimicro. Agents and Chemother. 13(1):34-40 (1978) . . 37

90. NEPHROTOXICITY OF GENTAMICIN. J Kosek, R Mazze, M Cousins. Lab. Invest. 30:48-57 (1974) 37

91. GENTAMICIN IN 1978. G Appel, H Neu. Ann. Intern. Med. 89:528-538 (1978) 38

92. QUANTITATIVE NEPHROTOXICITY OF GENTAMICIN IN NONTOXIC DOSES. B Trollfors, K Alestig, I Krantz, R Norrby. J. Infect. Dis. 141(3):309-309 (1980). 38

93. INTRAAORTIC BALLOON COUNTERPULSATION WITH AND WITHOUT REPERFUSION FOR MYOCARDIAL INFARCTION SHOCK. M DeWood, R Notske, G Hensley, J Shields, W O'Grady, J Spores, M Goldman, J Ganji. Circ. 61(6):1105-1112 (1980) 38

94. THROMBOXANE RELEASE DURING PACING-INDUCED PECTORIS: POSSIBLE VASOCONTRICTOR INFLUENCE ON THE CORONARY VASCULATURE. R Lewy, L Wiener, P Walinsky, A Lefer, M Silver, J Smith. Circ. 61(6):1165-1171 (1980) 39

95. PROSTAGLANDINS AND CARDIOVASCULAR FUNCTION: SOME BIOCHEMICAL AND PHYSIOLOGICAL ASPECTS. A Wennmalm. Scand. J. Clin. Lab. Invest. 39:399-405 (1979) 39

96. TEMPERATURE: A CRITICAL FACTOR DETERMINING LOCALIZATION AND NATURAL HISTORY OF INFECTIOUS, METABOLIC, AND IMMUNOLOGICAL DISEASES. D Rodbard, H Wachslicht-Rodbard, S Rodbard. Perspect. in Biol. and Med. 23:439-474 (1980). 40

97. INFLUENCE OF ENDOGENOUS OPIATES ON ANTERIOR PITUITARY FUNCTION. D Van Vugt, J Meites. Fed. Proc. 39(8):2533-2560 (1980). 41

98. SHOCK KIDNEY. A Bohle, S Mackensen-Haen, K Grund, H Christ, E Knöpfle, S Schellhorn. Path. Res. Pract. 165:212-220 (1979). . 41

99. THROMBOXANE A2 IN BLOOD VESSEL WALLS AND ITS PHYSIOLOGICAL SIGNIFICANCE: RELEVANCE TO THROMBOSIS AND HYPERTENSION. A Ally, D Horrobin. Prostagland. and Med. 4:431-438 (1980) . . . 42

100. THE DIFFERENTIAL INHIBITION OF PROSTAGLANDIN SYNTHESIS IN PLATELETS AND VASCULAR TISSUE IN RESPONSE TO ASPIRIN. B Shaikh, S Bott, L Demers. Prostagland. and Med. 4:439-447 (1980) 42

101. DIRECT MEASUREMENT OF LEUKOCYTE MOTILITY: EFFECTS OF PH AND TEMPERATURE. G Nahas, M Tannieres, J Lennon. Proc. Soc. Exp. Bio. and Med. 138:350-352 (1971). 42

102. PULMONARY HYPERTENSION IN SEPSIS. W Sibbald, N Paterson, R Holliday, R Anderson, T Lobb, J Duff. Chest Chest 73(5): 583-591 (1978) 43

103. EFFECT OF GLUCAGON ON GASTROINTESTINAL BLOOD FLOW OF DOGS IN HYPOVOLEMIC SHOCK. J Bond, M Levitt. Am J. Physiol. 238: G434-G439 (1980) 43

104. GENTAMICIN NEPHROTOXICITY IN THE DOG: SEQUENTIAL LIGHT AND ELECTRON MICROSCOPY. Vet Pathol. 17:206:217 (1980). 44

105. THE EFFECT OF *ESCHERICHIA COLI* ENDOTOXINS AND ADRENOCORTICAL HORMONES ON PLASMA ENZYME ACTIVITIES IN THE DOMESTIC FOWL. M Curtis, H Jenkins, E Butler. Res. Vet. Sci. 28:44-50 (1980). 44

106. REACTIVITY OF CEREBROCORTICAL VASCULATURE AND ENERGY METABOLISM TO DIRECT CORTICAL STIMULATION IN HAEMORRHAGIC SHOCK. E Dora, A Kovach. Acta Physiol. Acad. Scient. Hung. 54(4):347-361 (1979). 45

107. MECHANISM OF TRAUMATIC SHOCK. R Hardaway III. Surg. Gynecol. Obstet. 151:65-69 (1980). 45

108. CHANGES OF BASIC BIOCHEMICAL INDICES IN RAT LIVER TISSUE AFTER INTRAPERITONEAL APPLICATION OF ENDOTOXIN. B Hejcmanova, Z Konickova, J Musil, J Moserova. Acta Chirurg. Plast. 21(3): 182-290 (1979) 46

1. Action of Histamine of the Mesenteric Microvasculature. J. Fox, F. Galey, and H. Wayland. Microvasc. Res. 19: 108-126, 1980.

The effect of known, reproducible doses of histamine (0.1-100 μg/ml base) on the permeability of the microvasculature of the cat and rat mesentery was examined in vivo using intravital fluorescence microscopy and in fixed sections from identifiable regions of the same tissue using electron microscopy. The percentage of animals in which extravasation of fluorescent serum albumin in response to histamine was observed was positively related to dose, with approximately half the animals responding to 2-5 μg/ml (rat) or 0.1-0.5 μg/ml (cat). Electron microscopy of sections of vessels exhibiting extravasation of fluorescent tracer in vivo revealed numerous gaps ranging in size from 0.5 to 1.0 μm between endothelial cells. Serial sections and computer three-dimensional reconstructions showed that these gaps occurred at endothelial junctions but with irregular geometry and involvement of "cords" of cytoplasm bridging some of the endothelial gaps.

2. Complement-Dependent Activation of Canine Platelets by Endotoxin and Collagen: In Vitro Studies. T. L. Murphy, F. B. Taylor III, I. M. Welsman, J. M. Gilliam, and F. B. Taylor, Jr. Clin. Immunol. Immunopath. 16: 57-71, 1980.

The response of canine platelets to endotoxin and collagen was studied in a system composed of gel-filtered platelets and recalcified plasma depleted of the vitamin K-dependent factors by barium sulfate adsorption. The platelet clumping which occurred in response to both agents required an intact complement system as demonstrated by studies using heat- or hydrazine-treated plasma in which the response was blocked by complement depletion but occurred when the complement system was reconstituted. Activation of the vitamin K-dependent factors with thrombin generation was not involved in this response. The platelet response to these agents differed in that collagen induced a morphological platelet "fusion" with degranulation, 5-(^{14}C)HT release, PF3 expression whereas endotoxin caused loose platelet adhesion without degranulation, 5-(^{14}C) HT release, or expression of PF3. In addition, endotoxin-induced platelet adherence did not block subsequent "fusion" induced by collagen. The use of a PGE_1-theophylline mixture or heparin defined further differences in these complement-dependent platelet responses. At levels of theophylline and PGE_1 which blocked collagen induced "fusion," 5-(^{14}C)HT release, and PF3 expression, adherence of platelets still occurred in response to endotoxin and collagen. Heparin blocked collagen-induced 5-(^{14}C)HT release in a dose-dependent manner at levels above those needed for anticoagulation without inhibiting endotoxin-induced platelet adhesion. These results suggested that complement is involved in the response of the canine platelets to both endotoxin and collagen, and given the differences in this response as defined above, different mechanisms are probably involved.

3. Mechanisms of Impaired Cardiac Function by Vasopressin. M.F. Wilson, D. J. Bracket, L. T. Archer, and L. B. Hinshaw. Ann. Surg. 191: 494-500, 1980.

The mechanisms by which elevated levels of vasopressin (ADH) in man and animals cause serious myocardial dysfunction, evidenced by arrhythmias, reduction in cardiac output and coronary blood flow, are not settled. Experiments were conducted in 16 isolated working left ventricles to examine their metabolic and hemodynamic responses to the infusion of vasopressin the the combination of vasopressin and epinephrine. Contractile performance was evaluated by analysis of positive dP/dt, contractile element velocities, and ventricular work-curves using stroke work/end-diastolic pressure. Relaxation parameters, including negative dP/dt and the early diastolic relaxation time constant, were also studied. Coronary blood flow was reduced 22% or less by vasopressin while cardiac output was maintained at a constant level. Myocardial oxygen consumption, lactate and potassium balances were determined from arterial and coronary sinus concentrations. Vasopressin produced myocardial dysfunction indicated by decrements in contractile and relaxation indices, without evidence of global ischemia. Epinephrine restored the mechanical performance to normal without significant change in coronary blood flow, myocardial oxygen consumption, or lactate and potassium balance.

4. Reticuloendothelial Clearance of Blood-borne Particulates: Relevance to Experimental Lung Microembolization and Vascular Injury. G. D. Niehaus, P. R. Schumacker, and T. M. Saba. Ann. Surg. 191: 479-487, 1980.

The rapid increase in sheep lung vascular permeability observed during Pseudomonas aeruginosa bacteremia may be due to embolization of the pulmonary microvasculature by blood-borne particulates. Since alterations in lung microvascular permeability during mild septicemia in sheep may reflect inefficient RES phagocytic clearance of bacteria as well as products of bacterial induced intravascular coagulation, the opsonic and phagocytic aspects of RES fuction in sheep (30-50 kg) were compared to other species. RES function was evaluated by both the clearance and relative organ uptake of gelantinized I^{131} RE test lipid emulsion and gelantinized colloidal carbon. Immunoreactive opsinic α_2SB glycoprotein levels were determined by electroimmunoassay. The phagocytic index for RES clearance of the gelantinized (500 mg/kg) test lipid in sheep was 0.019 ± 0.002 corresponding to a half-time of 16.65 ± 1.74 minutes. With colloidal carbon (64 mg/kg), the phagocytic index in sheep was 0.080 ± 0.026, corresponding to a half-time of 6.16 ± 1.99 minutes. The per cent of injected lipid emulsion (%ID) in major RE organs, on a total organ basis (TO), was: liver = 15.69 ± 1.65%; spleen = 2.09 ± 0.78%. Localization in the lung = 31.39 ± 6.2%. The per cent of carbon localized in major RE organs (%ID/TO) was: liver = 21.37 ± 1.9%; spleen = 1.95 ± 0.55%. Localization in the lung = 32.70 ± 4.55%. In contrast, clearance and organ distribution of the blood-borne test microparticles in rats and dogs at the same relative challenging dose revealed a much more intense and rapid liver and spleen RES uptake with minimal lung localization (1-2%). Immunoreactive opsonic protein concentrations varied greatly with species and directly correlated with efficiency of RES function.

Levels observed were: dog = 1285 ± 135 μg/ml; mouse = 1077 ± 67 μg/ml; rat = 400 ± 31 μg/ml; human = 297 ± 10 μg/ml; and sheep = 184 ± 13 μg/ml. After intravenous particulate challenge, circulating immunoreactive opsonic protein in the sheep was depleted ($p < 0.05$) rapidly with partial recovery at 24 hours and mild rebound hyperopsonemia at 48 hours. This pattern is in contrast to the rapid restoration seen in dog and rat within three to six hours postchallenge. Thus, in sheep, the extensive pulmonary localization of blood-borns microparticles appears related to inefficient RES clearance function mediated by a relative deficiency of circulating opsonic protein (plasma fibronectin).

5. Graded Intestinal Vascular Obstruction: I. Description of an Experimental Shock Model in the Rat. E. Haglind, U. Haglund, O. Lundgren, M. Romanus, and T. Schersten. Circ. Shock 7: 83-91, 1980.

   The aim of this study was to standardize a model allowing studies of mechanisms of importance for developing irreversible shock. The model should also be suitable for studying the effects of different modes of treatment. Graded obstruction of the intestine and its vascular supply in rats was induced with a hydrostatic pressure cuff. Three levels of obstruction pressure were used: 50, 100, and 120 cm water. Mortality increased from 0% in control groups to 75% in the highest pressure group. Increases in hematocrit occurred in all groups. Mucosal lesions, including total destruction of villi, were more severe in the two highest pressure groups, and the degree of mucosal lesion correlated with mortality. This shock model was developed to allow studies of factors of importance for survival. One such factor is the degree of mucosal lesion.

6. Effect of Hemorrhagic Shock on the Performance, O_2-Consumption, and Ultrastructure of Isolated Rat Hearts. G. Rubanyi, A.G.B. Kovách, E. Koltay, T. Nagy-Dóra, I. Balogh, and E. Somogyi. Circ. Shock 7: 59-70, 1980.

   Rat hearts were isolated from control animals anesthetized and sham treated for 2.5 hours and following 2.5 hours of hemorrhagic hypotension and they were perfused by modified Langendorff technique. Hearts isolated following hemorrhagic hypotension exhibited increased coronary resistance, depressed left ventricular mechanical performance, and significantly increased sensitivity to threefold elevation of perfusate Ca^{2+} (from 1.3 to 3.9 mM). Electron microscopic examination showed increased permeability of the plasma membrane for lanthanum, zonal lesions of contractile filaments, damage of mitochondria, and dilation of T-tubules and sarcoplasmic reticulum. Experimental results indicate that myocardial damage is of hypoxic/ischemic origin during the procedure used as a model for shock. Mechanical failure of postoligemic hearts may be caused by the combination of zonal lesions of the myofilaments, damage of energy production, and impairment of cellular calcium metabolism.

7. Blockade of Opiate Receptors With Naloxone Improves Survival and Cardiac Performance in Canine Endotoxic Shock. D. G. Reynolds, N. J. Gurll, T. Vargish, R. B. Lechner, A. I. Faden, and J. W. Holaday. Circ. Shock 7: 39-48, 1980.

   The endogenous opiate β-endorphin is released by a variety of stressful situations. Since the cardiovascular system is quite sensitive to

exogenous and endogenous opiates, we tested the hypothesis that endorphins are involved in the pathophysiology of endotoxic shock by using the specific opiate antagonist, naloxone. Anesthetized adult mongrel dogs were given E. coli endotoxin 0.1 mg/kg intravenously at t = 0. This dose is 80% lethal at t = 24 hours. At t = 15 minutes the dogs were treated with either naloxone (n=6) 2 mg/kg intravenously as a bolus followed by 2 mg/kg·hr as an infusion intravenously until t = 4 hours or saline (n=14) in equivalent volumes. Endotoxin decreased cardiac output (CO) to 1.1 ± 0.2 liters/min, left ventricular contractility (LV) dp/dt_{max} from 2.2 ± 0.3 to 1.2 ± 0.1 X 10^3 mm Hg/sec, and mean arterial pressure (MAP) from 139 ± 3 to 68 ± 8 mm Hg. Naloxone prevented the decrease in LV dp/dt, attenuated the decrease in MAP, and reversed the fall in CO due to endotoxin. Naloxone in nonendotoxic dogs had little or no effect on cardiovascular parameters except for a slight but significant increase in MAP (n=5). Five of the six dogs treated with naloxone at 2 mg/kg survived, compared to only three of 14 saline-treated dogs ($P < 0.04$). Naloxone at 1 mg/kg improved cardiovascular parameters but did not improve survival. The improved survival and cardiac performance in canine endotoxic shock with naloxone suggests the involvement of endorphins or opiate receptors in the cardiovascular pathophysiology of endotoxic shock.

8. Naloxone Reversal of Hypovolemic Shock in Dogs. T. Vargish, D. G. Reynolds, N. J. Gurll, R. B. Lechner, J. W. Holaday, and A. I. Faden. Circ. Shock 7: 31-38, 1980.

The endogenous opiate ligand, β-endorphin, is released during stress. We tested the hypothesis that endorphins may be involved in the pathophysiology of hemorrhagic shock by using the opiate receptor blocking agent, naloxone. Two groups of five anesthetized dogs were instrumented to monitor cardiovascular performance and subjected to a protocol in which they were bled into a revervoir to lower mean arterial pressure to 45 mmHG and maintained at that pressure for one hour. At that time the revervoir was clamped and one group of dogs received an intravenous bolus of naloxone (2 mg/kg) and an infusion at 2 mg/kg·hr. These dogs demonstrated a prompt increase in arterial pressure, left ventricular dp/dt_{max} and cardiac output. The shed blood was returned at t = 2 hr and drug infusion continued for 2 hours. The control group of dogs received saline in equivalent volume. The control dogs died within 30 minutes of clamping the reservoir while all five treated dogs survived beyond 72 hours ($P < 0.02$). These data suggest the involvement of endorphins acting on opiate receptors as part of the pathophysiology in this shock model.

9. Reduced Myocardial Response to Calcium During Endotoxin Shock in the Cat. DJ McCaig and JR Parratt. Circ. Shock 7: 23-30, 1980.

The hemodynamic effects of short intravenous infusions of calcium chloride were examined in anaesthetized cats before and during shock induced with E. coli endotoxin (2 mg/kg). In normal cats calcium (5 mg kg^{-1} min^{-1} or 10 mg kg^{-1} min^{-1} infused for 5 minutes) increased left ventricular (LV) dP/dt_{max}, LVdP/dt at fixed isovolumic pressures, systemic arterial blood pressure and, usually, cardiac output. These hemodynamic changes lasted approximately 20 minutes. During endotoxin shock the calcium response (cardiac output, LVdP/dt, blood pressure) was greatly reduced. This diminished

responsiveness was evident as early as 0.5-1 hour after endotoxin and lasted throughout the 4-hour shock period. The duration of the hemodynamic response was also decreased during shock. Reduced myocardial sensitivity to a number of cardiac stimulants, including β-adrenoceptor stimulants and agents augmenting cellular cAMP/levels, occurs in this and other shock models. The present results suggest that this altered sensitivity is attributable to changes in the actual contraction processes rather than β-adrenoceptor desensitization or a defect in the cAMP system. Since this altered calcium response does not occur in vitro the results might suggest the presence, in shock, of a circulating agent acting at the level of cellular calcium exchange.

10. Continuous Intraperitoneal Antibiotic Lavage In The Management of Purulent Sepsis Of The Pelvis. M Moukhtar, and S Romney. Surg. Gynecol & Obstet., 150: 548-550, 1980.

    Fourteen patients with generalized purulent peritonitis of gynecologic origin were treated intraoperatively and postoperatively by continuous peritoneal lavage with an antibiotic solution in conjuction with conventional surgical management. Lavage was maintained for a period of 16 to 36 hours. This proved to be a safe and highly effective method. No major complications were encountered.

11. Effects of Endotoxin on Biosynthesis of Prostacyclin by Isolated Rabbit Peritoneum. H Bult, M Rampart, C Van Hove, and AG Herman. Arch. Int. Pharmacodyn. 242: 288-290, 1979.

    Blood levels of 6-oxo-$PGF_{1\alpha}$, the stable non-enzymic metabolite of prostacyclin, increase during endotoxin-induced hypotension. This could be due to enhanced biosynthesis or decreased enzymic metabolism of prostacyclin (Bult et al, 1978). Therefore we studied whether endotoxin influenced the biosynthesis of prostacyclin *in vitro* by rabbit peritoneum, which is a richer source of prostacyclin forming activity than rabbit aorta.

12. *In Vitro* Influence of Endotoxin on Human Mononuclear Phagocyte Structure and Function. 2. Enhancement of the Expression of Cytostatic and Cytolytic Activity of Normal and Lymphokine-activated Monocytes. J Hammerstrom. Acta path. microbiol. scand. 87: 391-399, 1979.

    The presence of non-toxic concentrations of *E. coli* endotoxin (LPS) during the *in vitro* interaction of normal human monocytes and a human tumour cell line (NHIK 3025) enhanced monocyte-mediated target cell cytostasis and cytolysis. Monocyte responsiveness to LPS was greatest at an intermediate state of *in vitro* differentiation. The expression of cytostatic and cytolytic activity by human monocytes activated with mediators from *Corynebacterium parvum*-stimulated human lymphocytes was also enhanced by LPS. Lymphokine activation did not induce additional LPS responsiveness in the monocytes. Monocytes activated with lymphokines and subsequently deactivated by *in vitro* culture did not show any increase in LPS responsiveness. A soluble cytostatic factor, which is probably not cold thymidine, was released from monocytes exposed first to lymphokines and then to LPS. While LPS is ineffective as an induction signal of monocyte cytotoxicity to tumour cells in this system, it enhances the expression of cytotoxicity induced by prolonged *in vitro* culture lymphokine activation.

13. *In Vitro* Influence of Endotoxin on Human Mononuclear Phagocyte Structure and Function. J Hammerstrom, and G Unsgaard. Acta path. microbiol. scand. 87: 381-389, 1979.

The effect of *E. coli* endotoxin (LPS) on human monocytes and peritoneal macrophages (PEC) during *in vitro* differentiation was studied. Short-term (<24 hours) exposure to LPS in concentrations up to 50 μg/ml did not affect monocyte survival or ^{51}Cr-release, but concentrations of 10 μg/ml or more reduced monocyte survival when LPS exposure was prolonged to 72 h. Undifferentiated monocytes seemed to be more sensitive to this effect. Monocyte and PEC protein synthesis was reduced by non-toxic LPS concentrations in both undifferentiated and differentiated cells. LPS exposure reduced monocyte ingestion and degradation of ^{125}I-labelled *Candida albicans*, dependent on time and dosage. The induction of monocyte and PEC-mediated cytostatic activity to tumour cells induced by prolonged *in vitro* culture was also impaired by LPS. The morphological alterations induced in mononuclear phagocytes by LPS included a changed distribution of cells in the monolayer, changes in membrane structure and apparent reduction of lysosomes. LPS thus interferes adversely with several aspects of human mononuclear phagocyte *in vitro* differentiation.

14. Fundamentals of clinical cardiology. Prevention of Cardiogenic Shock. JS Geddes, AAJ Adgey, and JF Pantridge. Am. H. J., 99: 243-254, 1980.

It is clear that further work is required to define the place of the more recently introduced regimes in the routine management of patients with myocardial infarction. It is, however, important to recognize that shock may usually be prevented by such simple measures as the timely relief of pain and the immediate correction of disturbances of heart rate and rhythm, and of blood pressure. Such disturbances commonly result from autonomic imbalance.

The crucial point in prevention of shock is the early initiation of therapy. Resources directed toward this end will undoubtedly result in greater reward than their direction toward complex circulatory support systems.

15. Endotoxemia of cirrhosis: An observation not substantiated. JT Fulenwider, C Sibley, SF Stein, B Evatt, BM Nordlinger, and GL Ivey. Gastroenterol 78: 1001-1004, 1980.

Physiologic similarities between cirrhotic and septic patients have implicated systemic endotoxemia as a possible mediator of the hemodynamic, neurologic, and hematologic complications observed in patients with cirrhosis of the liver. The recently reported high prevalence of endotoxin in ascites, as well as in portal and systemic plasma, has further incriminated endotoxin of gut origin as the responsible agent. Limulus amebocyte lysate tests were performed upon peripheral plasma of 38 cirrhotic patients; portal plasma and ascites were assayed in 14 and 11 of these patients, respectively. No endotoxin was detectable. We believe that the ubiquity of endotoxin, with the attendant opportunities for specimen contamination, is the most likely explanation for the recently reported high prevalence of endotoxin in the plasma and ascites of cirrhotic patients.

16. The role of prostaglandins in endotoxemia: Comparisons in response in the nonpregnant, maternal, and fetal models I. Prostaglandins and the pulmonary effect of experimental endotoxemia. RC Cefalo, PE Lewis, WF O'Brien, JR Fletcher, and PW Ramwell. Am. J. Obstet. Gynecol. 137: 53-57, 1980.

The mechanism of respiratory distress in sepsis is unknown. Previous work has shown elevations of prostaglandins during sepsis. This study reveals a correlation between levels of prostaglandins $F_{2\alpha}$ and E and pulmonary hypertension and other parameters of respiratory distress in oophorectomized ewes subjected to endotoxin. The use of prostaglandin synthetase inhibitors prior to endotoxin prevented the rise in prostaglandins and the development of respiratory distress.

17. Improved prognosis for Granulocytopenic Patients with Gram-Negative Bacteremia. LJ Love, SC Schimpff, CA Schiffer, and PH Wiernik. Am. J. Med., 68: 643-648, 1980.

The grave prognosis associated with gram-negative bacteremia occurring in granulocytopenic patients with cancer suggests that granulocyte transfusions are frequently indicated. We have evaluated 67 episodes of gram-negative bacteremia, studied in four consecutive antibiotic trials, in order to correlate prognostic determinants of recovery. These patients had a median absolute granulocyte count of 100/μl at the time of bacteremia. Empiric antibiotic regimens were begun at the first evidence of suspected infection. Granulocyte transfusions were employed only as clinically indicated by inadequate patient response to antibiotic therapy. Among the 29 patients who had an increase in their granulocyte count of > 100/μl over the subsequent 14 days, 27 (93 per cent) recovered whereas among 38 patients who had no appreciable increase in their granulocyte count, 21 (55 per cent) improved ($p = 0.006$). In this latter group of patients with no granulocyte recovery, the susceptibility of the pathogen(s) to the initial empiric antibiotic regimen was of major importance. None of four patients responded when the pathogen was resistant to both antibiotics initially utilized, six of 14 (44 per cent) patients responded when there was susceptibility to one antibiotic, and 15 of 20 (75 per cent) patients responded when there was susceptibility to both antibiotics ($p < 0.025$). We conclude that patients with gram-negative bacteremia and persistent granulocytopenia will often respond to antimicrobial therapy alone provided the initial choice of empiric antibiotics is appropriate and that their use is instituted promptly. Granulocyte transfusions need not be added unless clinical evaluation indicates inadequate response.

18. Hypoglycemia as a Manifestation of Sepsis. SI Miller, JR Wallace, Jr., IM Musher, EJ Septimus, S Kohl, and RE Baughn. Am. J. Med., 68: 649-654, 1980.

Hypoglycemia has rarely been described as a clinical sign of severe bacterial sepsis. We recently encountered nine patients in whom hypoglycemia (mean serum glucose of 22 mg/dl) was associated with overwhelming sepsis. Clinical disease in these patients included pneumonia and cellulitis; in three patients, no focus of infection was apparent. Altered mental status, metabolic acidosis, leukopenia, abnormal clotting studies and bacteremia were common features in these cases. In four patients, no cause for hypoglycemia other than sepsis was present. In five patients, another possible metabolic cause for hypoglycemia was present (alcoholism in four and chronic renal insufficiency in one) although none had been observed to be hypoglycemic on previous hospitalizations.

Streptococcus pneumoniae (three cases) and Hemophilus influenzae, type b, (two cases) were the most common pathogens, and the over-all mortality was 67 per cent.

The mechanism(s) for hypoglycemia with sepsis is not well defined. Depleted glycogen stores, impaired gluconeogenesis and increased peripheral glucose utilization may all be contributing factors. Incubation of bacteria in fresh blood at room temperature does not increase the normal rate of breakdown of glucose suggesting that the hypoglycemia occurs in vivo. Hypoglycemia is an important sign of overwhelming sepsis that may be more common than has previously been recognized.

19. Protection from Oxygen Toxicity with Endotoxin. Role of the Endogenous Antioxidant Enzymes of the Lung. LFJ Summerville, and D Massaro. J. Clin. Invest. 65: 1104-1110, 1980.

Endotoxin treatment of adult rats before hyperoxic exposure significantly increases their survival rate in >95%O_2. In this study, we wished to determine: (a) whether endotoxin would protect against O_2 toxicity if it were administered after the animals were already in >95% O_2 for 12-48 h; and (b) the relationship between the endogenous antioxidant enzymes of the lung and the protective effect of endotoxin treatment.

Our results showed that adult rats given a single 500 µg/kg dose of endotoxin up to 36 h after the onset of O_2 exposure had significantly increased survival rates and decreased lung fluid accumulation compared to untreated animals in O_2 ($P < 0.05$). (Survival, 16/49 (untreated rats); 18/20 (endotoxin at 12 h after the start of O_2 exposure); 25/25 (endotoxin-24 h); 15/20 (endotoxin-36 h).)

Endotoxin-treated animals in O_2 showed increases in pulmonary superoxide dismutase, catalase, and glutathione peroxidase activities before the usual time of onset of measurable pulmonary edema in untreated animals in O_2. When diethyldithiocarbamate was used to block the superoxide dismutase enzyme rise in the endotoxin-treated rats in O_2, the protective action of endotoxin against pulmonary O_2 toxicity was nullified. In endotoxin-treated, O_2-exposed mice, there were no lung antioxidant enzyme increases, and no protective effect from O_2 toxicity was achieved.

We conclude that in the rat, a single dose of endotoxin given even 36 h after the onset of hyperoxic exposure results in marked protection against O_2-induced lung damage, and the increased lung antioxidant enzyme activity in the endotoxin-treated rats appears to be an essential component of this protective action.

20. Pretreatment with Methylprednisolone Shortens Survival in a Canine Model of Pseudomonas Pneumonia. JD Katz, PG Barash, MD Tilson, W Gersoff, AR Gutnazu, AE Baue. J. Surg. Res. 28: 260-268, 1980.

The effectiveness of steroids in reducing the pulmonary damage of aspiration or endotoxemia is controversial. The following study was undertaken to test the hypothesis that steroid pretreatment beneficially influences cardiopulmonary function and survival in a standardized model for canine pseudomonas pneumonia. Thirty mongrel dogs were anesthetized (pentobarbital, pancuronium), intubated, and ventilated (10 cc/kg X 10/min) for 24 hr

with 50% O_2/50%N_2O. Fourteen of the dogs were pretreated with methylprednisolone (30 mg/kg). The remaining 16 dogs received no steroids. Half of the animals in each group were ventilated with positive and expiratory pressure (10 cm H_2O) (PEEP), and half with zero and expiratory pressure (ZEEP). Sixteen of the animals received an endotracheal inoculation of pseudomonas. Statistically significant deterioration of physiological parameters was evident in infected, steroid-treated animals as early as 2 hr. These pronounced changes were delayed until 8 hr in the animals managed without steroids. The administration of steroids did not appear to enhance the integrity of the alveolar capillary membrane. The overall mortality for the infected animals was 75% with steroid treatment versus 38% without steroid. We conclude that methylprednisolone (30 mg/kg) offers no advangage in terms of cardiopulmonary performance or survival in this experimental model of canine pseudomonas pneumonia and endotoxemia. In fact, this evidence suggests that steroid pretreatment may be detrimental.

21. Lung Lysosomal Enzyme Release during Hemorrhagic Shock and Endotoxemia. RH Demling, R Proctor, N Duy, and JR Starling. J. Surg. Res. 28, 269-279, 1980.

Lysosomal enzymes are felt to be released during hemorrhage and endotoxin from ischemic splanchnic viscera and from leukocytes sequestered in the lungs. It is hypothesized that these enzymes then produce endothelial cell damage. Lysosomal enzymes are generally found at highest concentration in lymph draining an injured organ. We determined the extent of ß-glucuronidase and aryl sulfatase release into blood and lung lymph during hemorrhagic shock and endotoxemia, correlating this with changes in pulmonary microvascular integrity. We found a 100% increase in plasma ß-glucuronidase during fatal hemorrhage but noted no change in the lung lymph concentration. Lung injury was also not seen. After *Escherichia coli* endotoxin, the plasma levels of both enzymes increased by 100%, while the lung lymph levels increased by 400-600%. A severe alteration in lung permeability was also seen. The actual transport of enzymes in lung lymph increased 20- to 40-fold. We therefore documented a strong correlation between lung injury and changes in lung lymph lysosomal enzyme content, while changes in plasma enzyme content reflected systemic injury.

22. Lung Fluid and Protein Dymanics During Hemorrhagic Shock, Resuscitation, and Recovery. RH Demling. Circ. Shock 7: 149-161, 1980.

Fluid and protein flow acress the pulmonary microcirculation was measured during hemorrhagic shock resuscitation and recovery using either blood or crystalloid as the resuscitation fluid. Fluid filtration rate (Q_f) and protein permeability were measured using, as reliable indicators, lung lymph flow and lymph protein content in the unanesthetized sheep with chronic lung lymph fistula. During shock, Q_f was maintained, probably because of an increase in pulmonary venous resistance. During resuscitation Q_f was significantly increased, but no increase in protein permeability was noted. This increase in Q_f was not affected by the type of resuscitation fluid, as the decrease in plasma oncotic pressure with crystalloid was compensated for by a decrease in the interstitial oncotic pressure. Crystalloid resuscitation did, however, increase the Q_f response to a fluid challange in the recovery period, whereas blood resuscitation did not.

23. Marrow Culture in Diffusion Chambers in Rabbits: III. Effect of Endotoxin and Leukocyte Products on Cell Production. R Willemze, RI Walker, JC Herion, and JG Palmer. Am. J. Heratol. 7: 33-43, 1979.

Soluble leukocyte products harvested from incubated peritoneal exudate leukocytes, injected intravenously or intramuscularly, increased production of granulocytes and macrophages in marrow in duffusion chambers implanted into the peritoneal cavity of rabbits. Red cell production in the chambers was not consistently affected. Endotoxin increased production of all cell types. Endotoxin tolerance induced by daily injection of endotoxin to host rabbits abolished granulopoietic stimulation by endotoxin given during the culture period but did not diminish the granulopoietic stimulation produced by injected leukocyte products. Attempts to induce tolerance to leukocyte products by daily injections did not reduce the granulopoietic stimulation produced by either endotoxin or leukocyte products injected during the culture period. Intraperitoneally administered leukocytes products markedly inhibited production of all cell types.

Endotoxin or leukocyte products given to normal rabbits increased plasma colony stimulating activity (CSA); the increase occurred sooner after leukocyte products than after endotoxin. Endotoxin-tolerant animals showed no rise in CSA after endotoxin, but their response to leukocyte products was normal. Leukocyte products added to agar cultures neither supported nor inhibited colony growth but augmented CSA-stimulated colony production. Endotoxin, Leukocyte products, and CSA are different and may interact in regulating granulopoiesis.

24. Hematologic Responses Inceded by Endotoxin in Normal and Endotoxin Tolerant Dogs. TJ MacVittie, and RI Walker. Exp. Hemat. 8: 599-609, 1980.

Tolerance to the release of colony-stimulating activity (CSA) following injection of endotoxin was induced in beagle dogs by repeated, daily i.v. injections of endotoxin for 5 consecutive days. Several hematologic parameters were studied during the induction of tolerance and to a single challenge dose of endotoxin at 10 days and 60 days post-tolerance. We studied circulating levels of CSA, granulopoietic activity of progenitor cells derived from marrow and peripheral blood as assayed by in vitro culture and in vivo duffusion chamber (DC) techniques, marrow M:E, and peripheral blood leukocyte and platelet levels.

The induction of CSA tolerance in the canine system was characterized by a marked increase in marrow granulopoiesis in association with a significantly diminished CSA response, both during induction of tolerance and through at least 10 days (but not 60 days) after induction of tolerance. Tolerant dogs responded to challenge doses of endotoxin with marked increases in marrow granulopoiesis, release of DC progenitors into the peripheral circulation, and more rapid return of peripheral leukocytes and platelets to normal levels. Although marrow granulopoiesis in tolerant dogs had returned to within normal values by 60 days after tolerance, their granulopoietic response to a challenge dose was significantly more rapid than normal dogs or tolerant dogs challenged at 10 days despite the reduced CSA. Increased capability to mobilize leukocytes can increase resistance to the biological effects of endotoxin. One function

of leukocytes is to reduce platelet aggregation in the microcirculation, thereby limiting the subsequent release of potentially deleterious mediators. Further knowledge of the hemtologic parameters responsive to endotoxin tolerance will aid in elucidating the mechanism of increased resistance to endotoxin challenge.

25. Renal Effects of Dopamine During Prolonged Hemorrhagic Hypotension in the Dog. RE Neiberger, JI Levin, and JC Passmore. Circ. Shock 7: 129-138, 1980.

Dopamine has been reported to increase renal blood flow during hemorrhagic shock. Since this effect would be of considerable benefit in shock, the effect of dopamine on hemorrhagic hypotension to 70 mm Hg for five hours was studied. Plasma renin activity and outer cortical blood flow were significantly greater in the group of dogs receiving dopamine. Total renal blood flow, sodium excretion, and potassium excretaion were similar in both groups; however, the ratio or urine sodium to potassium concentration followed closely the plasma renin activity. We conclude that dopamine infusion alone is of limited value in improving renal hemodynamics and function during hemorrhagic hypotension to 70 mm Hg. In addition, increased plasma renin activity produced by dopamine infusion during hemorrhage would tend to offset the expected increases in renal blood flow and sodium excretion.

26. Monitoring Hepatic Dysfunction during Intravenous Hyperalimentation. BJ Rowlands, BV MacFadyen, P DeJong, and SJ Dudrick. J. Surg. Res. 28: 471-478, 1980.

Abnormalities of routine biochemical liver function tests may occur during intravenous hyperalimentation (IVH) with hypertonic dextrose and amino acid solutions. The mechanisms are uncertain but it has been proposed that cyclic hyperalimentation may protect against abnormalities at high calorie:nitrogen ratios. Four dogs received IVH at a calorie: nitrogen ratio of 162:1, 288:1 (continuous), and 288:1 (cyclic). Each regimen was given for 3 weeks, was isonitrogenous, and maintained body weight and nitrogen equilibrium. Hepatic function was assessed at the beginning and end of each regimen using routine liver function tests, and in addition, indocyanine green clearance and amino acid molar ratio (AAMR). Gyclic hyperalimentation did not protect against the development of hepatic dysfunction. No changes occurred in total bilirubin concentration. Glutamic pyruvate transaminase and AAMR may give an earlier indication of subclinical deterioration of hepatic function than glutamic oxaloacetic transaminase, alkaline phosphatase, and indocyanine green clearance during IVH regimen, and may be the most useful indices for sequential monitoring of hepatic dysfunction.

27. Response of the pulmonary microcirculation to fluid loading after hemorrhagic shock and resuscitation. RH Demling, M Manohar, and JA Will. Surg. 87: 552-559, 1980.

We compared the response of the pulmonary microcirculation to fluid overload before and 24 hours after hemorrhagic shock, resuscitated with either blood or crystalloid, to determine whether vascular permeability was altered, making the lung more susceptable to fluid overload after shock and whether this response differed depending on the type of resuscitation fluid. Fourteen unanesthetized sheep with chronic lung lymph fistula were given a fluid challenge (one half of blood volume)

before and 24 hours after hemorrhagic shock. Seven sheep were resuscitated after shock with shed blood and seven sheep were resuscitated with Ringer's lactate alone equal to 2.5 times the amount of shed blood. Pulmonary vascular pressures and lung lymph flow Q_l were at baseline in both groups 24 hours after resuscitation except for the decreased plasma oncotic pressure πp in the crystalloid group. Interstitial oncotic pressure, πi was also lowered in this group such that the gradient (πp-πi) remained at baseline. In the blood group, pulmonary vascular pressures and Q_L increased transiently after fluid loading before and after shock with the mean time for Q_L to return to baseline being 5.5 and 5.9 hours for the preshock and postshock periods, respectively. In the crystalloid group, fluid loading after shock produced an increase in pulmonary vascular pressures resulting in a significant increase in Q_L over the preshock fluid response with the mean time for Q_L to return to baseline being 10.1 hours. However, changes in the value of (πp-πi) were identical to those seen before shock. Therefore we noted that 24 hours after shock, lung permeability was not significantly altered but crystalloid resuscitation did make the lung more susceptible to volume overload.

28. Diagnosis and Treatment of Cannula-related Intravenous Sepsis in Burn Patients. BA Pruitt, WF McManus, SH Kim, and RC Treat. Ann. Surg. 191: 546-553, 1980.

Supperative thrombophlebitis was identified in 193 (4.2%) of 4,636 burn patients treated during the years 1960-1978. A single vein was involved in 162 patients, while 31 had multiple vein involvement. The distribution and incidence of suppuration in individual veins reflected the frequency of cannulation, with an increase in the use of central vein cannulae, during the last 10 years, paralleled by a rise in central vein suppuration. The infecting organisms reflected the patients' surface flora. Local signs of infection were present in less than half (35%) of the patients and recovery of a positive blood culture in a clinically septic patient was the most frequent clinical presentation prompting exploration of previously cannulated veins. Pathogenetic mechanisms are identified and criteria defined for determining the extent of excision necessary. Ninety veins were excised from 75 patients during the 1969-1978 period, of whom 30 (40%) survived (three other patients with antibiotic treated central vein disease also survived). Treatment failure was attributable to inadequate excision in 12 patients, suppuration within another unexcised vein in eight patients, hematogenous dissemination of infection in five patients in whom the local disease had been eradicated, and other disease in 20 patients. Prophylaxis must emphasize limited duration of cannulation. Timely diagnosis and treatment can effect maximum salvage and reduce the likelihood of systemic dissemination.

29. Liberation of Endotoxin from *Escherichia coli* by Addition of Antibiotics. H Goto, S Nakamura. Japan. J. Exp. Med. 50: 35-43, 1980.

The liberation of endotoxin from *Escherichia coli* by the addition of antibiotics was investigated using a new method of limulus test, i.e. dry up method. The addition of the bactericidal antibiotic, amino-benzylpenicillin or streptomycin sulfate, to the suspension of

Escherichia coli (about 10^6/ml) increased the concentration of endotoxin in the suspension about eight to nine times during a 3-hour period after the addition of antibiotic accompanying with the concomitant decrease of viable cell counts. The addition of the bacteriostatic antibiotic, tetracycline hydrochloride, also increased the indotoxin level, but this increase was rather mild. On the other hand, in the case of the addition of polymyxin B sulfate, there was no evident increase of the endotoxin level. This ability of polymyxin, i.e. the ability to suppress the elevation of endotoxin levels, was shown when polymyxin in the concentration of more than 2.5 μg/ml was added against about 10^6/ml *Escherichia coli* and was also shown by the combinational use of polymyxin with aminobenzylpenicillin or streptomycin. Furthermore, the endotoxin-inactivating ability of polymyxin was shown in the study where extracted lipopolysaccharide was used in place of viable cells.

30. Blood Levels of 6-Oxo-Prostaglandin $F_{1\alpha}$ During Endotoxin-Induced Hypotension in Rabbits. H Bult, J Beetens, AG Herman. Europ.J. Pharmacol. , 63: 47-56, 1980.

Levels of 6-oxo-prostaglandin $F_{1\alpha}$ (6-oxo-$PGF_{1\alpha}$), the non-enzymic degradation product of prostacyclin, were measured in arterial blood from anaesthetized rabbits, before and after intravenous (i.v.) administration of endotoxin (Lipopolysaccharide W E. coli 0111:B4, 5mg/kg). 6-Oxo-$PGF_{1\alpha}$ was assessed by radioimmunoassay after extraction and separation by thin-layer chromatography. The basal concentration of 6-oxo-$PGF_{1\alpha}$ in blood was less than 100 pg/ml in 19 out of 20 rabbits. This indicates that the level of circulating prostacyclin is generally below 100 pg/ml. The administration of endotoxin induced a biphasic hypotension, and increased levels of 6-oxo-$PGF_{1\alpha}$ were found in all endotoxin-treated aminals during the secondary hypotension after 60 and 120 min. Pretreatment with indomethacin (2.5 mg/kg) prevented the secondary fall in arterial blood pressure and significantly suppressed the rise in 6-oxo-$PGF_{1\alpha}$. However, indomethacin (2.5mg/kg) prevented the secondary fall in arterial blood pressure and significantly suppressed the rise in 6-oxo-$PGF_{1\alpha}$. However, indomethacin failed to alter the endotoxin-induced thrombocytopenia and did not modify the endotoxin-induced platelet aggregation in vitro. It is concluded that prostacyclin contributed to the secondary hypotension which accompanied the i.v. administration of endotoxin. Thromboxane A_2 seems not to be of primary importance in the endotoxin-platelet interaction.

31. Endotoxin-Enhanced Secretion of Macrophage Insulin-Like Activity. JP Filkins. J. Retriculo. Soc. 27: 507-511, 1980.

Peritoneal exudate macrophages induced in male Holtzman rats with sodium caseinate produced a mediator with insulin-like activity as assessed by the conventional bioassay of increased glucose oxidation in epididymal fat pads. *Salmonella enteritidis* endotoxin increased secretion of macrophage insulin-like activity (MILA) either a) when the endotoxin was added directly to acute cultures of macrophages co-incubated with epididymal fat pads in Krebs-Ringer bicarbonate buffer containing

5.5 mM D-glucose and 5.0 μCi/ml of U-D-^{14}C-glucose or b) when it was incubated with macrophage cultures in Dulbecco's modified Eagle's medium and subsequent bioassays of the conditioned media. It is postulated that MILA may play a role in the characteristic hypoglycemia of endotoxin shock.

32. In Vitro Phagocytosis by *Limulus* Blood Cells. PB Armstrong, and J Levin. J. Invert. Path. 34: 145-151, 1979.

Limulus blood cells maintained in culture are able to phagocytose particles under conditions where bacterial endotoxin is absent. In the presence of endotoxin, phagocytosis is inhibited because the cells are immobile under these conditions and because the extracellular gel found in the presence of endotoxin prevents cell-particle contact. It is suggested that *Limulus* blood cells respond to Gram-nagative organisms by the formation of an extracellular gel matrix that entraps the bacteria and handles other types of foreign particles by phagocytosis.

33. Septic Shock. LE Gelin, I Dawidson, U Haglund, M Heideman, and H Myrvold. Surg. Clin. N. Am. 60: 161-174, 1980.

Septic shock is still largely an unsolved problem in regard to both an understanding of the mechanisms involved and the management of therapy. Bacteremic shock as described by Waisbren has been extensively studied experimentally with endotoxin, exotoxin, and live bacteria.

Shock may be the primary manifestation of a virulent infection of a wound or the urinary tract, biliary tract, gastrointestinal tract, or lungs. However, shock is more severe as a secondary manifestation due to sepsis as a complication of delayed or unsuccessful treatment of primary hypovolemic shock after major injuries. This may occur many days after the primary shock and often leads to multiple organ failure.

There are several predisposing factors in both medical and surgical patients that impair the defense mechanisms of the host, such as advanced age, systemic disease, dehydration, and hypovolemia; immunosuppressive and cytotoxic drug treatment, and iatrogenic infections from indwelling catheters and tracheostomies.

34. Pulmonary Edema-Hypoxia and Overperfusion. NC Staub. New Eng. J. Med. 302: 1085-1087, 1980.

Lately, interest in the causes of increased-permeability edema has shifted to the role of circulating blood factors: fibrin, platelets or leukocytes. In our studies, we have found the presence of polymorphonuclear leukocytes to be essential if increased-permeability edema is to result from pulmonary emboli produced with glass beads. In line with this requirement for leukocytes, there have been reports that leukocyte infiltrations may be found in the lungs of patients dying from high-altitude pulmonary edema. But the relation between overperfusion of parts of the lung, raised pulmonary vascular pressure, alveolar hypoxia, and neutrophils has not been settled. One can only speculate about the importance of the fact that, in the patients described by Hackett et al., the pulmonary overperfusion had been present since birth.

35. Endogenous pyrogen release by fetal sheep and pregnant sheep blood leukocytes. NW Kasting, WL Veale, KE Cooper. Can. J. Physiol. Pharmacol. 57: 1453-1456, 1979.

These experiments were undertaken to determine if fetal blood leukocytes are capable of producing endogenous pyrogen (EP), as neither the fetal nor newborn lamb can produce a fever in response to bacterial endotoxin. Maternal leukocytes were also tested for their ability to produce EP as the near-term pregnant sheep cannot produce a fever in response to bacterial endotoxins or EP. The results demonstrate that both fetal and near-term maternal leukocytes can produce EP, thus supporting experimental evidence that the inability of the newborn and near-term mother to become febrile is due to a process other than lack of EP production.

36. Genetic Control of Peripheral Leukocyte Response to Endotoxin in Mice. MW Verghese, M Prince, R Snyderman. J. Immunology. 124: 2468-2473, 1980.

Many *in vitro* effects of lipopolysaccharide (LPS) on murine B cells and macrophages are known to be controlled by a single genetic locus. In the present study we measured changes in the number of circulating leukocytes at various times after LPS administration as in *in vivo* manifestation of endotoxin susceptibility and found that these responses also were under strict genetic control: mice from the endotoxin susceptible strain C3HeB/FeJ responded with a 50% drop in circulating leukocytes 3 hr after a dose of 0.75 μg LPS whereas nearly 100 times this amount of LPS was required for a comparable change in resistant C3H/HeJ mice. Thus, peripheral leukopenia was a very sensitive discriminator between the two strains in comparison to LD_{50} measurements, in which strain differences are reported to be 10- to 20-fold. These readily detectable strain differences in response to LPS could well be exploited to determine LPS contamination where false-positive Limulus tests are obtained. Intact LPS was a much more potent inducer of leukopenia than either base-hydrolyzed LPS of lipid A unless lipid A was properly solubilized. The kinetic and the dose response to LPS of peripheral leukocytes in F_1 hybrid offsprings from these two strains was indistinguishable from that of the susceptible C3HeB/FeJ parent, thus suggesting a dominant mode of inheritance for this trait. Dominant inheritance of this *in vivo* trait was confirmed by backcross analysis.

37. Pathophysiology of *Candida albicans* Meningitis in Normal, Neutropenic, and Granulocyte Transfused Dogs. HS Chow, SC Sarpel, and RB Epstein. Blood, 55: 546-551, 1980.

Candida albicans meningitis was induced in normal dogs and in dogs rendered neutropenic (< 500/cu mm) in order to follow cerebrospinal fluid (CSF) granulocyte migration patterns, quantitative fungal cultures, and clinical events. Dogs received an intrathecal challenge with 10^7 *C. albicans* and CSF samples were monitored. Neutropenia was produced by administration of cyclophosphamide 5 days before fungal challenge. Granulocytes for transfusion were obtained from normal doners by semicontinuous centrifugation. In normal dogs, CSF neutrophilic pleocytosis began 3 hr after fungal challenge and reached a maximum within 24 hr. These

dogs cleared their infection and remained clinically well. Nontransfused neutropenic dogs failed to show granulocyte responses in CSF and died within 84 hr of meningitis. In a controlled study of 8 pairs of neutropenic dogs, one partner received a single granulocyte transfusion 24 hr following fungal challenge. Transfusions were followed by significant increments ($p<0.025$) in CSF pleocytosis compared to controls that correlated with concurrent peripheral blood increments ($r=0.8$). Six of eight transfused dogs survived longer than their nontransfused partners. Four dogs that had received prior immunization with donor tissue failed to show CSF granulocyte increments following transfusion. It was concluded that: (A) the model provides for assay of *in vivo* kinetics of transfused granulocytes during a local infection, (B) in normal dogs the initial CSF granulocyte response is associated with resolution of the infection; (C) transfused granulocytes migrate into the CSF in proportion to peripheral blood increments; and (D) infusion of granulocytes into sensitized recipients demonstrates no biologic effect.

38. Control of Arterial Pressure and Renal Function During Glucocorticoid Excess in Dogs. JE Hall, CL Morse, MJ Smith, DB Young, and AC Guyton. Hypertension, 2:139-148, 1980.

This study was designed to investigate the long-term effects of glucocorticoids on the control of mean arterial pressure (MAP) and renal function. Infusion of 10 mg/day of methylprednisolone (MP), a glucocorticoid with minimal mineralocorticoid activity, for 10 days in six intact conscious dogs maintained on a sodium intake of 78 mEq/day resulted in a decrease in MAP of 98 ± 1 to 89 ± 2 mm Hg, a decrease in sodium iothalamate space to 89 ± 2% of control, and a marked increase in glomerular filtration rate (GFR) effective renal plasma flow (ERPF), and urinary sodium excretion. Chronic infusion of MP at doses of 2-800 mg/day in four dogs maintained on low (5 mEq/day) or high sodium intakes (160-223 mEq/day) also caused increases in GFR and ERPF, as well as natriuresis and decreased sodium iothalamate space, while causing either no change or a slight reduction in MAP. To determine whether glucocorticoids potentiate the chronic effects of angiotensin II (AII) on MAP and renal function, MP was infused in dogs undergoing AII infusion (5 ng/kg/min). During AII hypertension, chronic infusion of 5 or 10 mg/day or MP also resulted in a marked renal vasodilation, natriuresis, and reductions in sodium iothalamate space, while causing small reductions in MAP. Thus, we found no evidence that chronic glucocorticoid excess causes hypertension in dogs, or that glucocorticoids potentiate the blood pressure or renal effects of AII. Instead, glucocorticoids tended to reduce MAP, probably because of chronic renal vasodilation, increased excretion of sodium, and volume depletion.

39. The Interaction of Leukocytes and Erythrocytes in Capillary and Postcapillary Vessels. GW Schmid-Schönbein, S Usami, R Skalak, and S Chien. Microvas. Res. 19: 45-70, 1980.

In capillaries white blood cells tend to flow with a lower velocity than red blood cells. This is due to the larger volume of the white cells and their spherical shape as compared to that of the red cells with their biconcave disk shape, as well as to the smaller deformation of the white cell during flow in narrow blood vessels. As a result, red blood cells often accumulate upstream of a white cell in a capillary with a single file of cells, whereas downstream of the white cell a red cell depleted region is formed. When the white cell enters a postcapillary vessel with increased diameter, the following red cells will pass the slower white cell and thereby displace it away from the vessel axis toward the wall. Then interaction between the white cell and the endothelium leads to adhesion, and the white cell starts rolling along the endothelium. We have investigated the detailed flow field in these small vessels with a large-scale hydrodynamic model of a capillary and a post-capillary vessel based on geometric and kinematic similarity. The capillary is simulated by a straight or divergent rigid axi-symmetric tube, and white cells are simulated by shperes, red cells by flexible disks, and plasma by a Newtonian fluid. The experiments show that, under the proper circumstances, hydrodynamic collision of a disk and a sphere in a narrow tube results in the disks passing the sphere, leading to the displacement of the sphere toward the tube wall. The model reproduces qualitatively the *in vivo* flow field, and the results indicate that the attachment of white blood cells in postcapillaries is augmented as a result of hydrodynamic interaction with red cells.

40. Another Look at Shock. WB Cannon. Path. Res. Pract. 165: 197-199, 1979.

This issue of "Pathology-Research and Practice" consists of papers which were read during the 12th Congress of the International Academy of Pathology in Jerusalem in 1978. Experiences acquired during daily routine work in the autopsy room has taught us that the shock-producing event and the related clinical picture of sepsis, or "septic shock", have become of major importance to clinicians and pathologists today. The etiology of shock has proved to be almost as difficult to elucidate as that of arteriosclerosis or neoplasia. The condition involves a large number of factors, does not clearly reveal its onset, and further develops in a manner that is only incompletely understood. The clinical symptoms of shock have been well known for a long time. Ambroise Pare described the state of shock as accompanied by a cold sweat, pallor and the absence of a detectable pulse. In 1741, Le Dran clearly defined the main shock-inducing event, i.e. the circulatory shock, in his book: "Traité ou Reflexions tirées de la Pratique sur les Playes d'Armes à feu", by stating: "Il est bien vrai que la circulation se fait encore librement dans tous les troncs et dans les branches moyennes; mais elle est suspendue dans toutes les subdivisions capillaires..." According to Le Dran this disturbance of the circulation explained the cold extremities of wounded soldiers who had become victims of shock. It is amazing how precisely the early clinicians observed signs and symptoms, and what accurate conclusions they were capable of drawing. So far as I know, the term "shock" was first used to describe the condition of surgical shock, as we understand the term today. The word is derived from the Dutch

"schokken", meaning to jolt, or jerk suddenly. Of course, a great deal is known today about the pathological and physiological features of the shock-producing event, and we are well-informed on the patho logical antomy of shock. However, many problems remain unsettled, particularly with regard to coagulation of the blood in victims of shock and the manifestations of the condition in the lung. The publications presented here are intended to contribute to the solution of these unsolved problems.

41. Plasma Catecholamine Levels and Pulmonary Dysfunction in Sepsis. JK Bocking, WJ Sibbald, RL Holliday, S Scott, and T Viidik. Surg. Gynecol. Obstet. 148: 715-719, 1979.

In a retrospective analysis of 18 patients iwth sepsis and adult respiratory distress syndrome, we found that high plasma epinephrine and noradrenalin levels were associated with severe defects on oxygenation that accompany this disease. The result of previous experimental work support the concept that high plasma catecholamine levels augment already existing defects in the ventilation to perfusion ratio and increases the measured intrapulmonary shunt fraction. The results of this study do not, however, delineate whether or not the relationship between high circulating plasma catecholamine levels and severe adult respiratory distress syndrome is causal or simply a measurement of two indexes which reflect the severity of the underlying disease process.

42. Documentation of Pulmonary Capillary Permeability in the Adult Respirator Distress Syndrome Accompanying Human Sepsis. RR Anderson, RL Holliday, AA Driedger, M Lefcoe, B Reid, and WJ Sibbald. Am. Rev. Resp. Dis. 119: 869-877, 1979.

Current evidence suggests that pulmonary edema accompanying human sepsis may result either from changes in the serum oncotic and hydrostatic pressures or an increase in the permeability of the pulmonary microvasculature. In this study, we compared the "clearance" of injected ^{131}I-labeled human serum albumin from blood to bronchoalveolar secretions in intubated patients with pulmonary edema secondary to sepsis or myocardial infarction. A significantly increased mean ± SE clearance of the radionuclide was seen in patients with sepsis (0.34 ± 0.03 ml per hour) compared to those with myocardial infarction (0.043 ± 0.008 ml per hour) ($P<0.001$), although both groups had similar degrees of edema on chest radiographs. Because the patients with sepsis had no severe decrease in serum oncotic pressure (18.4 ± 5.0 mm Hg) or evidence of left heart failure, as determined by the pulmonary wedge pressure (11.0 ± 6.8 mm Hg), we concluded that the genesis of the pulmonary edema in sepsis was due to an increase in pulmonary microvascular permeability, as measured by the increased clearance of ^{131}I-labeled human serum albumin.

43. Enhancement of Leukocyte Activity Against Escherichia coli After Brief Exposure to Chloramphenicol. H Pruul, and P McDonald Antimicrob. Agents Chemotherop. 16: 695-700, 1979.

The effect of brief exposure of Excherichia coli to chloramphenicol on the antibacterial activity of normal human leukocytes was studied by following changes in viability of the bacteria in the presence of leukocytes and serum. Growth was suppressed, and the extent of suppression was directly related to the period of exposure and the concentration of chloramphenicol. When exposed to clinically achievable levels of the drug for 10 min., E. coli failed to resume normal growth for 1 to 4 h in the presence of leukocytes and serum after removal of the drug. The post-antibiotic leukocyte enhancement effect required the presence of antibody and complement. This effect demonstrates the importance of early events in the encounter between antibiotic and microorganism in determining the subsequent activity of host defense components.

44. Endotoxin-induced Changes in the Rabbit's Blood Picture. Z Konickova, Z Likovsky, and L Pavkova. Physiol. Bohemoslov. 29: 81-87, 1980.

Changes in the blood picture - specifically leukopenia followed by leukocytosis and thrombocytopenia - are constant manifestations of experimental endotoxaemia. According to the data in the literature, the greatest shifts in the white blood component occur directly after the administration of endotoxin and during the next 24 hours, but there are discrepancies in the actual particulars.

45. The relationship of Glucagon and Insulin to Sequential Changes in Metabolic Fuel Utilization in Shock. CD Wood, Y Bentz, M Martin, WO Read. J. Surg. Res. 28: 239-245, 1980.

Previous studies in the dog have demonstrated significant alterations in the mobilization of metabolic fuel during shock. In particular, mobilization of depot fat is markedly depressed. The present study examines the sequential utilization of nonlipid fuels over a 24-hr shock period. Metabolic rates were unchanged from controls. Skeletal muscle glycogen fell exponentially from 7.0 ± 0.5 to 2.7 ± 0.2 mg/g ($P<0.001$) after 24 hr of shock. Protein breakdown as reflected by urea production was linear throughout the period and increased 50% over controls ($P<0.001$). Lactate levels did not reflect changes in metabolic rate but fell to nearly normal levels once muscle glycogen was depleted. The contribution of CHO and protein combined to CO_2 production fell from 70% in early shock to 42% in the final 12 hr of 24-hr shock period. This compares to 23% in controls. Protein catabolism alone accounted for an average of 32% CO_2 production in shock. While insulin levels rose slightly in early shock and then fell, glucagon rose rapidly in the first 5 hr of shock and then remained significantly and constantly elevated throughout the entire shock period. The insulin-glucagon molar ratio remained in the severely catabolic range throughout.

46. Wedge Balloon Catheter Angiography in the Critical Care Unit. MS Lefcoe, JW Sibbald, and RL Holliday Crit. Care Med. 7: 449-453, 1979.

In order to visualize pulmonary vascular drainage and to assess its influence on measurements obtained by Swan-Ganz catheters in the wedge position, 75 patients were examined with a portable chest x-ray after injection of water soluble contrast medium into a Swan-Ganz catheter in the wedge position. In normal patients and patients with left-sided cardiac failure, the pulmonary vein draining the wedged segment was easily visualized. However, in many patients with sepsis and ARDS, the pulmonary vein was poorly visualized or not visualized. In some of these patients, there was a high pulmonary wedge pressure. It is hypothesized that in some of these patients, the competitive flow system between the pulmonary and bronchial circulation is upset due to a decrease in flow through pulmonary vessels and either relative or absolute increase in bronchial flow in the segment distal to the balloon. This increase in the ratio of bronchial to pulmonary blood flow results in dilution of the contrast medium by the nonopacified bronchial blood. The decreased pulmonary blood flow may be due to a vasospastic factor in either the small pulmonary arterioles or venules as, in two cases, the pulmonary vein was visualized after injection of vasodilators. In order to eliminate these misleading false high wedge pressures (WP) in these types of patients, the authors recommend that wedged Swan-Ganz catheter angiograms be performed in selective cases. If the pulmonary vein is not visualized and there is elevation of the pulmonary WP, this must not be taken as a sign of elevated left-sided cardiac pressure. If the pulmonary vein is visualized, the WP measured can be considered to reflect the left-sided cardiac pressure.

47. Glucocorticoid Binding to Normal and Activated Alveolar Lung Cells. SC George, PW Gudewicz, and RC Jaffe. Lung 157: 57-64, 1980.

The presence of specific, high affinity, low capacity glucocortoid binding was demonstrated in resident and activated rabbit lung macrophage suspensions. The binding of $|^{3}H|$-dexamethasone reached a plateau after 2 h at 30°C. Scatchard analysis revealed only a single class of binding sites in both activated and nonactivated macrophages. There was no significant difference in the dissociation constants for the binding of dexamethasone to nonactivated and activated macrophages ($4.39 \pm 2.53 \times 10^{-9}$ vs. $1.08 \pm 0.36 \times 10^{-9}$M). The number of binding sites in activated macrophages (15,900 ± 1,710 binding sites per cell), however, was significantly greater than the number of binding sites in nonactivated machrophages (5,260 ± 490 binding sites per cell). The relative binding activities of steroids for the receptor were dexamethasone ≈ triamcinolone acetonide > cortosol > corticosterone > progesterone ≈ testosterone > 17β-estradio. Thus, a specific glucocorticoid receptor exists in nonactivated and activated lung macrophages. The presence of activation is associated with a large increase in the number of specific glucocorticoid binding sites per cell.

48. Beneficial Actions of Imidazole in Endotoxin Shock. EF Smith, III, JH Tabas, and AM Lefer. Prostagland. Med. 4: 215-222, 1980.

The effects of imidazole were studied in anesthetized cats during endotoxin shock. Imidazole (25 mg/hg/hr) was administered 30 minutes after intravenous injection of E. coli endotoxin (5 mg/kg). The degree of the severity of the shock state was assessed by mean arterial blood pressure (MABP), and by plasma cathepsin D and MDF activities. Analysis of thromboxane B_2 concentrations during shock was also performed by radioimmunoassay. Administration of imidazole to cats given endotoxin partially prevented the decrease in MABP of endotoxin shock. Imidazole significantly prevented the increase in plasma cathepsin D and MDF activities. Thus, infusion of imidazole resulted in metabolic and hemodynamic improvement during endotoxin shock. The mechanism of imidazole protection appears to be via lysosomal membrane stabilization, stimulation of cardiac function and possibly by antagonizing the biochemical effects of endotoxin administration, rather than by inhibition of thromboxane synthesis. Data obtained using imidazole to block thromboxane synthesis in shock states must be interpreted with caution.

49. The effect of endotoxin shock on histamine and histodine decarboxylase enzyme activities in various tissues of cats. S Saleh, NG Waton and JR Parratt. Proc. B.P.S., December,308P, 1979.

The present study is an attempt to correlate early cardiovascular changes following endotoxin administration and blood and tissue levels of histamine and histamine-forming enzymes in cats. *E. coli* endotoxin (Difco Laboratories, 055:B5) in a dose of 2 mg/kg suspended in saline, was injected *intravenously* over a period of 40-45 seconds. Blood Pressure and blood histamine were determined at one, three, five, and ten minutes. There was a marked and progressive decrease in systemic arterial pressure reaching as low as 58 mm Hg (normal 120 ± 6 mm Hg) within three minutes. This was followed by a partial recovery after five and ten minutes

50. Gram-Negative Sepsis in Neonates: A Nursery Outbreak Due to Hand Carriage of Citrobacter diversus. M.F. Parry, J.H. Hutchinson, N.A. Brown, Chii-Huei Wu, and L. Estreller. Ped. 65: 1105-1109, 1980.

An outbreak of Citrobacter diversus infections occurred in a newborn nursery at a 350-bed community hospital during September and October 1978. Two infants developed sepsis and meningitis and nine additional infants had asymptomatic umbilical colonization. These infants did not differ from control, noncolonized infants with respect to numerous clinical and environmental variables. Surveillance cultures failed to implicate an environmental source for the Citrobacter. However, cultures of nursery personnel identified a handcarrier whose removal eliminated neonatal colonization with C diversus and decreased the number of isolates of certain other enteric bacteria found on umbilical stumps. Factors implicated in the perpetuation of the carrier state in this nurse included marked dermatitis from repeated hand washing and hand care practices involving the overnight use of plastic gloves and nutritive hand cream. The mode of transmission within the nursery appeared to be from nurse's hands to infant's umbilicus. Use of triple dye on umbilical stumps and chlorhexidine hand washing preparations did

not eliminate this cycle. Surgical manipulation of colonized umbilical stumps may have been responsible for illness in two infants.

51. Pathophysiology of Shock. H Haljamäe, B Amundson, U Bagge, I Jennische, and PI Brånemark. Path. Res. Pract. 165: 200-211 1979.

Circulatory shock is a complex cyndrome which severly distrubs the homeostasis of the entire organism. It may be caused by such different conditions as hemorrhage, trauma, dehydration, septicemia, anaphylaxis or acute heart failure. According to current definitions, the common, pathyphysiological denominator in shock is an acute failure of the circulation to meet the nutritive demands of vital tissues. As a result of this hemodynamic distrubance, functional and structural changes occur in the organs affected. It follows that despite obvious differences in pathogenetic events, depending upon type of shock, basic similarities in tissue reaction to shock should exist regardless of cause. In this survey we will examine the sequence of events occurring during hypovolemic shock caused by hemorrhage or dehydration.

52. Blood Coagulation and Shock. T Saldeen. Path. Res. Pract., 165: 221-252, 1979.

This report describes how a finding at the autopsy table led to the observation of a clinical syndrome. A synthesis of autopsy experience, clinical investigations, and experimental and biochemical studies were able to shed light on one factor in the pathogenesis of this syndrome, namely blood coagulation with pulmonary microemboli and release and delayed elimination of peptides from fibrin degradation extravascularly in the lungs. These peptides may both induce increased permeability in the microcirculation and stimulate fibroblast proliferation. Knowledge about the pathogenesis has led to improved prophylaxis and therapy and a reduction of the number of deaths.

53. Morphologic Development of Human Shock Lung. UN Riede, CH Mittermayer, H Friedburg, K Wybitul, W Sandritter. Path. Res. Pract. 165: 269-286, 1979.

In the initial phase of shock, edema spreads throughout the alveolar interstitium even before injury occurs in the alveolar epithelium and endothelium. The endothelium and the epithelium are damaged only subsequently, causing reduction in the average barrier thickness of the epithelium and the endothelium. A point of irreversibility is reached by the end of the first week. While early cell regeneration may be observed within the alveolar endothelium and epithelium, proliferation of fibroblasts and fibrosis of the alveolar wall occur in addition to edema which spreads within the interstitium. This widening of the gas exchange barrier may be considered as the anatomic substrate of respiratory insufficiency induced by shock. This enlargement continues up to the moment when thickening of the alveoli impedes satisfactory functioning of the lung, and, as consequence, threatens the life of the patient.

54. Experimental Studies on Coagulation-Fibrinolytic Activity of White Blood Cells Influenced by Endotoxin. N Sakuragawa, K Takahashi, M Yoshiyama, C Jimbo, K Niiya, M Matsuoka and Y Ohnishi. Thromb. Res. 8: 887-891, 1976.

For the treatment of malignant disease and leukemia, many drugs, for instance, adrenocortical steroids, 6-mercaptopurine and anti-inflammatory drugs, are used. These have inhibitory effects on the immunological mechanisms and function of white blood cells. Severe infection is complicated in these cases. Disseminated intravascular coagulation syndrome (DIC) is often observed in such cases with endotoxin shock. In this paper, we discuss the effects of endotoxin on the coagulation-fibrinolytic activities of white blood cells by *in vitro* and *in vivo* studies.

55. Age-Related Differences in Thermoregulatory Responses to Endotoxin In Rabbits. M Szekely and Z Szelenyi. Acta Physiol. Acad. Scient. Hung. 54: 389-399, 1979.

E. coli endotoxin evokes fever in rabbits immediately after birth. In 0-3 day-old rabbits the fever is monophasic and brown fat thermogenesis is mainly responsible for the reaction. In 6-10 day-old animals the fever is usually biphasic and increased heat conservation also contributes to the response. An inverse relationship exists between the endotoxin dose and the latent period before the onset of fever, while the height of the fever is independent of the endotoxin dose. The response is similar as that of adult rabbits, except that after all endotoxin doses the latent period is longer and the magnitude of the response slightly smaller in the newborn.

56. Reactivity of the Cerebrocortical Vasculature and Energy Metabolism to Direct Cortical Stimulation in Haemorrhagic Shock. E Dóra, and AGE Kovách. Acta Physiol Acad. Scient. Hung., 54: 347-361, 1979.

Direct electrical stimulation of the cerebral cortex was used to determine the changes of cortical carbohydrate and oxidative metabolism and of vascular reactivity during haemorrhagic shock. The results were as follows.

Electrical stimulation of the brain cortex applied in the control period led to a marked vasodilation and NAD reduction that was preceded in part of the experiments by a transient NADH oxidation. It is suggested that the increase in cortical NADH fluorescence observed during direct stimulation is due to the fact that the rate of cytoplasmic NADH production exceeded the rate of mitochondrial NADH oxidation and of the rate of H^+-transport from the cytoplasm into the mitochondria.

The cerebrocortical vascular and NAD/NADH redox state responses induced by electrical stimulation changed in the early hypovolaemic phase of shock. At this time, electrical stimulation of the brain cortex led to NADH oxidation in the majority of the experiments or in some experiments, the stimulation did not bring about changes in the redox state of the cortex. The total loss of the reactivity to direct stimulation of the cerebrocortical vessels and of energy metabolism preceded the occurrence of cortical ischaemia during the hypovolaemic phase of shock.

Since after reinfusion of the shed blood, redox state and vasculature remained unresponsive to stimulation even in those experiments in which cortical ischaemia improved, it is concluded that the carbohydrate and oxidative metabolism of the brain cortex were already irreversibly damaged in the early phase of hypovolaemic shock.

57. Intracellular Oxygen Tension and Energy Metabolism in the Cat Brain Cortex During Haemorrhagic Shock. AGB Kovách and E Dóra. Acta Physiol. Acad. Scient. Hung., 54, 333-346, 1979.

The changes in intracellular oxygen tension and energy metabolism of the cat brain cortex were studied by surface fluororeflectometry during haemorrhagic shock. The results may be summarized as follows.

Intracellular exygen tension, i.e. the maximum cortical NAD reduction obtained during nitrogen gas inhalation decreased gradually during the hypovolaemic phase of shock and finally, the brain cortex became ischaemic.

Partial uncoupling of the cerebrocortical mitochondrial respiration and oxidative phosphorylation appeared in the very early period of bleeding, as indicated by the overshot of the cortical NAD/NADH redox state towards oxidation subsequent to the cessation of nitrogen gas inhalation. Partial uncoupling of mitochondrial respiration and oxidative phosphorylation became more pronounced during the later phases of bleeding, finally, the mitochondrial electron transport stopped. In line with these changes the frequency and the amplitude of ECoG decreased gradually and markedly during the hypovolaemic phase of shock.

Microcirculation and energy metabolism of the cat brain cortex were severely and irreversibly damaged during the hypovolaemic phase of shock. This was clearly shown by the fact that in the majority of experiments the nitrogen anoxia after reinfusion failed to bring about changes in the cortical NAD/NADH redox state and the ECoG changes occurred during bleeding did not improve after reinfusion.

It is concluded that the early disturbances of cerebrocortical energy metabolism play an important role in the development of neural and vascular lesions of the brain that occur during haemorrhagic shock.

58. Myocardial Relaxation. II. Hemodynamic Determinants of Rate of Left Ventricular Isovolumic Pressure Decline. WH Gaasch, AS Blaustein, CW Andrias, RP Donahue, and B Avitall. Am. J. Physiol. 239: H1-H6, 1980.

The hemodynamic determinants of the time constant of left ventricular (LV) isovolumic pressure (P) decline were studied in 32 anesthetized dogs. The time constant, τ (an index of LV relaxation) was determined from the best exponential fit of the equation $P=P_o e^{-t/2}$ to LVP measured at 5-ms intervals during isovolumic relaxation; P_o=LVP at maximum negative dP/dt and t=time. At a constant heart rate of 120 beats/min, τ was determined during steady-state increases in preload (volume expansion), increases in afterload (methoxamine infusion),

reductions in afterload (nitroprusside infusion), and in variably afterloaded beats at a constant preload (single-beat interventions). τ was directly related to LV systolic pressure and length during the alterations in LV loading conditions, but τ was not closely related to the extent of fiber shortening. *During isoproterenol infusion*, relaxation was more rapid ($\downarrow\tau$), and following the administration of propranolol, relaxation was prolonged ($\uparrow\tau$). While data from the variably afterloaded contractions indicate the presence of systolic load-dependent LV relaxation velocity, the steady-state studies do not exclude the possibility that altered contractility through reflex or other mechanisms contributes to the observed changes in τ.

59. Response of Systemic Arterial Input Impedance to Volume Expansion and Hemorrhage. JP Dujardin, DN Stone, LT Paul, and HP Pieper. Am. J. Physiol. Soc. 238: H902-H908, 1980.

Experiments on 12 anesthetized dogs were performed to study the effects of changes in blood volume on the pulsatile hemodynamics of the arterial system as seen from its input. Pressure and flow were measured in the ascending aorta under control conditions, after volume expansion with dextran 70 (+30% of estimated blood volume), and after hemorrhage (-15% of estimated blood volume). The input impedance of the arterial system was calculated for each condition. It was found that after volume expansion the characteristic impedance of the proximal aorta, Z_C, was decreased by 26.6 ± 5.1%(SE) ($P < 0.01$). After hemorrhage Z_C was increased by 30.4 ± 3.4% ($P<0.01$). Since it is well known that Z_C is a very weak function of the mean arterial pressure, it is concluded that the changes in Z_C seen with volume expansion or hemorrhage are caused mainly by changes in aortic smooth muscle activity. This conclusion is also supported by direct measurements of aortic pressure diameter relationships in earlier work from our lab.

60. Effect of Shigella flexneri Endotoxin on Ureagenesis and Liver Ultrastructure in Rabbits. M. Yoshino. Exp. Mol. Path. 32: 253-263, 1980.

Shigella Flexeri endotoxin (1 mg/Kg) was injected intravenously into rabbits in order to evaluate hepatotoxicity and effects on ammonia metabolism of the endotoxin. Blood ammonia level was significantly higher in the endotoxin-poisoned rabbits than in the control rabbits 24 hr after the rabbits received the endotoxin or saline. Urea production was measured *in vitro* using liver homogenates obtained from the endotoxin-poisoned and the control rabbits. No significant difference in the *in vitro* ureagenesis was found between the endotoxin-poisoned and the control rabbits, when the assay mixture for the ureagenesis contained all the components required for the measurement. However, omission of adenosine triphosphate (ATP) and the ATP-generating system from the urea production in the endotoxin-poisoned rabbits than in the control rabbits. Thus, derangement of energy metabolism in the hepatocytes seems to be one of the factors contributing to the high blood ammonia level observed in the endotoxin-poisoned rabbits. The liver ultrastructure of the endotoxin-poisoned rabbits showed swelling of hepatocytic mitochondria, deposition

of fine fat droplets in the cytoplasm of hepatocytes, bleb formation of hepatocytic membrane and atrophy of endothelial cells 24 hr after the rabbits received the endotoxin. These observations indicate that Shigella flexneri endotoxin is hepatotoxic in nature and it can cause reduced ammonia clearance by the liver.

61. The dynamics of the Lung Fluid Filtration System in Dogs with Edema. MH Gee and JA Spath. Circ. Res. 46: 796-801, 1980.

We studied the relationship between pulmonary microvasculature fluid filtration pressures and lung lymph flow rate (Q_l) as filtration pressures increased to determine why lungs with functional lymphatics become edematous and, as filtration pressures decreased, to determine the effect of edema formation onlymphatic function. Edema was induced by rapid intravenous infusion of neutralized Ringer's solution in a volume equivalent to 30% of body weight in seven anesthetized dogs. Pulmonary microvascular pressure (Pmv) and Q_l increased to 58 cm H_2O and 40 ml/hr, respectively, during the infusion. Initially, Q_l increased slowly and the estimated net fluid filtration pressure (Σ_p) increased rapidly with infusion. Later in the 30-minute infusion period, small increases in Σ_p produced greater changes in Q_l. Over a 3-hour postinfusion period, Pmv and Q_l decreased, but they remained significantly greater than baseline levels. During the postinfusion period, Q_l was a linear function of Pmv and a logarithmic function of Σ_p. Extravascular lung water content, measured postmortem, was 70% greater than normal. The relationship between Q_l and Σ_p during and after the infusion demonstrated marked hysteresis. These results suggest that extravascular fluid accumulated in the lung in part because the lymphatics responded relatively slowly to rapid increases in Σ_p. Furthermore, the data suggest that, although the lymphatics may not be a quantitatively important route for removal of edema fluid, the pressure-volume characteristics of the pulmonary interstitium seem to have a major influence on lymphatic function.

62. Lung Tissue Volume During Development of Edema in Isolated Canine Lungs. CR Felton, and WG Johanson. J. Appl. Physiol.: 48: 1038-1044, 1980.

The technique of estimating pulmonary tissue volume (Vt) by rebreathing a tissue-soluble gas is rapid and noninvasive. We examined the sensitivity of this technique for the estimation of Vt in isolated, perfused canine lungs during the development of pulmonary edema. Vt was 84 ± 15% (mean ± SD) of the associated lung weight for lung weights of up to 240% of base line but decreased to 70 ± 2% when the lung weight exceeded 510% of base line. Small rebreathing tidal volumes resulted in significantly smaller values for Vt in edematous lungs. An abrupt increase in pulmonary venous pressure increased lung weight due to vascular distensions; Vt measurements detected less than half of this increase, implying that certain portions of the intravascular blood volume are not measured by this technique.

63. Limitations of Lactate Production as an Index of Myocardial Ischemia. CS Apstein, F Gravino, and WB Hood, Jr. Circ. 60: 877-888, 1979.

The relationship between myocardial lactate production and the severity and duration of ischemia was studied in globally ischemic, isolated rat and rabbit hearts. In both species, the rate of lactate production was not constant, despite a constant degree of ischemia; the coronary venous lactate concentration reached a peak value 10-15 minutes after the onset of ischemia and then decreased by 40-50% during 15-60 minutes of sebsequent ischemia. The rate of lactate production in moles/min (concentration X flow rate) was decreased during more severe degrees of ischemia, despite an increase in venous lactate concentration. Maximum lactate production occurred with mild-to-moderate ischemia; during severe ischemia, lactate production was reduced 88% in the rat and 71% in the rabbit myocardium.

A model of regional ischemia was constructed using the rates of lactate production determined in the globally ischemic, isolated hearts. Even under ideal conditions of a "steady-state" degree of ischemia and optimal placement of the coronary sinus sampling catheter, calculated changes in the coronary sinus lactate level did not show a constant or directionally similar relationship to modeled changes in the ischemic condition. Our results indicate that indices of lactate metabolism may not reliably measure sequential changes in the amount or degree of ischemia.

64. Changes in Serum Lipid in Endotoxin-Poisoned Mice. S Sakaguchi, and O Sakaguchi. Microbiol. Immunol. 24: 357-360, 1980.

In previous papers (6, 7) we reported that the administration of endotoxins from *Salmonella typimurium* and *Vibrio parahaemolyticus* resulted in a marked increase in the level of serum triglycerides in mice. The level of serum-free fatty acids (FFA) exhibit an early transitory increase 1-3 hr after injection of endotoxin, but was lower after 16-24 hr than in fasting control mice. Total phospholipid levels in the serum and liver of poisoned mice were not appreciatly different from those of control mice. Coran et al (1) reported that baboons subjected to shock showed hypoinsulinemia and a significant decrease in serum FFA. Groves and his co-workers (5) found an increase in the level of serum triglycerides in dogs with bacteremia. This study was undertaken to see whether or not the administration of the single sublethal dose of endotoxin to mice can alter the lipid constituent in the blood.

65. Effect of coronary sinus occlusion on coronary pressure-flow relations. RF Bellamy, HS Lowensohn, W Ehrlich, and RW Baer. Am. J. Physiol. 239: H57-H64, 1980.

We studied the effect of transient occlusion of the coronary sinus on the relationship between aortic pressure and circumflex coronary blood flow in open chest anesthetized dog preparations during artificially prolonged diastoles. The coronary pressure-flow relation was linear, and flow stopped at an arterial pressure ($P_{f=0}$) that always exceeded coronary venous pressure (P_{cv}). During reactive hyperemia, $P_{f=0}$ was

31 mmHg when P_{cv} was 5 mmHg and increased to 52 mmHg when the coronary sinus was occluded (P_{cv}, 38 mmHg). Elevation of P_{cv} translated the coronary pressure-flow relation to a higher $P_{f=0}$ without altering the slope of the relation. $P_{f=0}$ increased by about two-thirds of the increase in P_{cv}. We found no evidence that there existed a level of P_{cv} below which changes in P_{cv} had no effect on the coronary pressure-flow relation. These data are not compatible with the existence of a vascular waterfall mechanism in the coronary circulation unless it is assumed that P_{cv} is one of the determinants of $P_{f=0}$.

66. The Interrelationship between Thromboxane Biosynthesis, Aggregation and 5-Hydroxytryptamine Secretion in Human Platelets in Vitro. LC Best, TK Holland, PBB Jones, and RGG Russell. Thromb. Haem., 43: 38-40, 1979.

Platelet aggregation, secretion of 5-hydroxy tryptamine and production of thromboxane B_2 were monotored simultaneously in human platelet suspensions in the absence and presence of cyclooxygenase of thromboxane synthetase inhibitors. Aggregation, secretion and thromboxane B_2 formation in response to either sodium arachidonate or epinephrine were blocked by aspirin or by 1-N-butyl imidazole suggesting that thromboxane biosynthesis was an essential requirement for platelet activation by these agents. In contrast, thrombin and collagen could apparently induce aggregation and secretion via two pathways: at low doses involving thromboxane production, but at higher doses by a direct mechanism independent of thromboxane biosynthesis. In the case of ADP, inhibition of thromboxane production blocked secretion but had little effect on aggregation, indicating that secretion was probably dependent on thromboxane biosynthesis which probably occurred as a result of aggregation. Thus it appears that although the processes of thromboxane production, release of dense granule constituents and aggregation may often be intimately linked, each process can occur independently of the other, depending upon the stimulus used.

67. The prostanoids in Hemostasis and Thrombosis. JB Smith. Am. J. Path. 99: 743-804, 1980.

The recent discovery and study of novel compounds derived from prostaglandin endoperoxides, referred to in this review as the prostanoids, has provided new insights into the mechanisms regulating the functions of blood platelets. Thromboxane A_2, discovered in 1975 by Hamberg, Svensson, and Samuelsson, is capable of inducing platelet aggregation and constricting blood vessel walls. Counterbalancing these effects, prostacyclin (PGI_2), discovered just one year later, acts to inhibit platelet aggregation and dilate the vessel wall. These properties, and the great facility with which platelets make thromboxane A_2 and endothelial cells make prostacyclin, implicate these novel prostanoids in both hemostasis and thrombosis. The purpose of this review is to bring together the many different aspects of this new area of research, which range from the consumption of essential fatty acids to the elevation of adenosine 3':5'-cyclic phosphate (cyclic AMP). A major aim will be to impress hte reader with the great potential that management of the production or effects of these prostanoids offers for the treatment of thrombosis.

68. Microvascular Architecture of Anthropoid Primate Intestine. KG Swan, EK Spees, DG Reynolds, JC Kerr, and MJ Zinner. Circ. Shock 5: 375-382, 1978.

Microvascular architecture of the small intestine of New World monkey, ape, and man was examined with the silicone rubber injection technique and the results compared to previous observations in dogs and Old Workd monkeys. In man, chimpanzee, and New World monkey the small intestine villus contains a single centrally located vein draining a subepithelial capillary plexus converging at the apex of the villus. These villi also contain a single eccentrically located artery rising to the midlevel of the villus, where it branches into subepithelial capillaries over the rest of its length. This vascular architecture most closely resembles that observed in the gut of Old World monkeys in which the villus artery is absent altogether. This observation contrasts the microvascular architecture of canine intestinal villi in which marginal arteries surround a centrally located vein. These patterns of microvascular anatomy are analyzed in terms of the role of the gut in pathogenesis of experimental shock. The differences observed may account for the known species variations in canine and primate experimental shock.

69. Morphologic Development of Human Shock Lung. UN Riede, CH Mittermayer, H Friedburg, K Wybitul, W Sandritter. Path. Res. Pract. 165: 269-286, 1979.

In the initial phase of shock, edema spreads throughout the alveolar interstitium even before injury occurs in the alveolar epithelium and endothelium. The endothelium and the epithelium are damaged only subsequently, causing reduction in the average barrier thickness of the epithelium and the endothelium. A point of irreversibility is reached by the end of the first week. While early cell regeneration may be ovserved within the alveolar endothelium and epithelium, proliferation of fibroblasts and fibrosis of the alveolar wall occur in addition to edema which spreads within the interstitium. This widening of the gas exchange barrier may be considered as the anatomic substrate of respiratory insufficiency induced by shock. This enlargement continues up to the moment when thickening of the alveoli impedes satisfactory functioning of the lung, and, as consequence, threatens the life of the patient.

70. Hemodilution, Oxygen Consumption, and Recovery From Shock. I Dawidson. 1: 7-86, 1980.

The present experiments describe hemodynamic function and oxygen transport in relation to survival and protein loss during experimental intestinal ischemic shock in dogs and rats, and compare the relative effectiveness of several plasma substitutes to reverse this shock.

71. The Functioning of Blood Platelets. MB Zucker. Sci. Am. 242: 86-103, 1980.

Outline of Journal Article. Platelets and Their Contents. Hemostasis. Platelet Aggregation. Secretion. Abnormal Platelet Function. Von Willebrand's Disease. Platelet Pathology. Therapy. Thrombosis. Platelets and Atherosclerosis.

72. Complement-Induced Granulocyte Aggregation. An Unsuspected Mechanism of Disease. HS Jacob, PR Craddock, DE Hammerschmidt, and CF Moldow. Sem. Med. Beth Israel Hosp. 302: 789-794, 1980.

The capacity of blood cells to aggregate, best exemplified by the response of platelets to vascular injury, is generally thought to be beneficial. However, if aggregation occurs inapproxpriately - that is, in a manner irrevelant to hemostasis - ischemic syndromes may result. The myocardial ischemia of Prinzmetal's angina pectoris, for example, may reflect platelet aggregation in coronary arteries. This article presents evidence that granulocytes as well as platelets aggregate intravascularly, and that the resultant and previously unsuspected phenomenon of leuko-embolization may underlie tissue damage in such diverse clinical situations as pulmonary dysfunction in hemodialyzed patients, sudden blindness with retinal infarction after trauma or acute pancreatitis (Purtscher's syndrome), myocardial infarction, and adult respiratory-distress syndrome.

73. Granulocyte Aggregation as a Manifestation of Membrane Interactions With Complement: Possible Role in Leukocyte Margination, Microvascular Occlusion, and Endothelial Damage. PR Craddock, DE Hammerschmidt, CF Moldow, O Yamada, and HS Jacob. Sem. in Hemat. 16: 140-147, 1979.

Activation products of the terminal complement cascade potently affect granulocyte function, inducing, for example, their migration toward (chemotaxis), and adherence to (opsonization), microbes, and stimulating their production of microbicidal oxygen radicals such as superoxide anion, and the like. We present studies that demonstrate that a C5-derived peptide, probably C5a, is a potent promoter of granulocyte and monocyte adhesion to endothelium (margination) and, in addition, causes granulocyte autoaggregation *in vitro* and *in vivo*. Although possibly beneficial by producing phagocyte clumps to mechanically entrap unwanted microbes, such aggregates may be deleterious, particularly if sustained, especially in the lung.

74. Association of Complement Activation and Elevated Plasma-C5a With Adult Respiratory Distress Syndrome. Pathophysiological Relevance and Possible Prognostic Value. DE Hammerschmidt, LJ Weaver, LD Hudson, PR Craddock, and HS Jacob. The Lancet May, 947-949, 1980.

Clinical and experimental observations suggest that aggregation of polymorphonuclear granulocytes (PMN) in response to activated complement (C) might contribute to the genesis of the adult respiratory distress syndrome (ARDS), aggregating PMN causing pulmonary dysfunction by becoming lodged in the lung as leucoemboli. PMN-aggregating activity can be detected in C-activated plasma and reflects C5a levels. In 61

patients at risk for ARDS a strong and highly significant correlation was found between the presence of PMN-aggretating activity in the plasma and development of ARDS; this correlation was also significant when patients with sepsis were excluded from analysis. In Patients followed prospectively detection of elevated C5a seemed to be a useful predictor of ARDS. Since Corticosteroids have been shown to inhibit PMN aggregation both *in vitro* and *in vivo*, the evidence for a role for PMN aggregation in the genesis of ARDS supports the use of corticosteroids in this disorder.

75. Aminoglycoside Nephrotoxicity: Comparative Assessment in Critically Ill Patients. ME Plaut, JJ Schentag, and WJ Jusko. J. Med. 10: 257-267, 1979.

In a prospective trial to determine the incidence of nephrotoxicity with each of three aminoglycoside antibiotics, adults in intensive care units with presumed or proven bacterial infections were treated with intravenous gentamicin, tobramycin, or amikacin. Treatment groups were similar with respect to age, other medical disorders, type of infection, duration of aminoglycoside therapy, additional antibiotics used, other drugs prescribed (notably diuretics and corticosteroids), and rate of superinfection. Nephrogentamicin, and tissue accumulation of drug seemed linked to nephrotoxicity, the use of gentamicin fell in one hospital (Buffalo General Hospital) as tobramycin was more widely employed. Amikacin was reserved for use in patients with infections due to multiply-resistant bacteria.

Once patients received at least 6 doses of an aminoglycoside, their courses were followed until death or discharge from the hospital. Nearly all doses of the drug were administered by the intravenous route. Dosing schedules were adjusted for both changes in kidney function and serum levels of drug. Multiple courses of aminoglycoside therapy in a given patient were assessed separately. A change in dosing schedule based on serum antibiotic levels was made by a pharmacokineticist (J.J.S.) not otherwise participating in patient care. Superinfection was defined as the isolation of a new pathogen in pure culture from blood, secretions, or urine in patients with recurrent fever and clinical signs of infection that began after the original pathogen was eradicated.

A clinician noted any rise in serum creatinine of 0.5 mg/dl or more during aminoglycoside therapy, or up to seven days thereafter. Nephrotoxicity was ascribed to the aminoglycoside used unless another cause, such as septic shock, was apparent. Evidence of damage to kidney tubules was not considered when assigning the cause of nephrotoxicity, even though such an assessment was underway. The clinician was purposefully unaware of the results of these kinetic studies. A "call" of aminoglycoside-related nephrotoxicity was not changed, once made, to avoid bias. Data were analyzed by the chi-square method.

76. Comparative Low-Dose Nephrotoxicities of Gentamicin, Tobramycin, and Amikacin. GH Hottendorf, and LL Gordon. Antimicrob. Agents and Chemotherap. 18: 176-181, 1980.

Most investigations of the comparative nephrotoxicities of aminoglycosides in animals have utilized large multiples of the human dose. Furtherfore, many of these assessments have used only one or two dose levels and have not described a dose-response comparison among antibiotics. Because of this lack of comparative dose-response data over a range of low multiples of the human dose, the nephrotoxicities of gentamicin, tobramycin, and amikacin were investigated in 180 rats, utilizing doses ranging from one to seven times the equivalent human clinical doses. Histopathological evaluations of both kidneys from each rat were scored without knowledge of the treatment, and statistical analyses of the results indicated that a linear and parallel dose-response relationship existed for each drug, the relative nephrotoxicity over the range of doses analyzed was gentamicin>tobromycin>amikacin ($P=0.0001$), and, unlike amikacin, the human dose equivalents (milligrams per kilogram) of gentamicin and tobramycin were significantly nephrotoxic in rats ($P<0.05$).

77. Effect of sepsis on tissue adenine nucleotide levels. IH Chaudry, KA Wichterman, and AE Baue. Surgery 85:205-11, 1979.

Tissue adenine nucleotides were measured in rats to determine if there is depletion of energy stores associated with sepsis. Peritonitis was produced by cecal ligation and cecal puncture. At 16 to 24 hours after ligation, rats which were lethargic but still normotensive (late sepsis) and showed clinical and laboratory confirmation of peritonitis-sepsis were stunned by a blow on the head, and small peices of tissue were removed and frozen. Adenine nucleotides were measured enzymatically. In late sepsis adenosine triphosphate (ATP) levels in liver and kidney decreased significantly; however, no significant decreases were observed in the diaphragm or gastrocnemius muscle. Hydrogen polarograph measurements of hepatic blood flow indicated that flow was decreased markedly at this stage of peritonitis. A second group of rats was prepared in the same manner, except they were studied 10 hours after ligation (early sepsis). Most rats at this stage of sepsis appeared to be only mildly ill; however, blood cultures obtained from six rats so prepared all were positive. These rats did not show any decrease in either hepatic blood flow or tissue adenine nucleotides. Thus the changes in adenine nucleotides observed in late sepsis (low-flow septic rats) are similar to those seen during early hemorrhagic shock and suggest inadequate perfusion associated with peritonitis as the cause.

78. Amino acid metabolism in dogs with *E. coli* bacteremic shock. LI Woolf, AC Groves, and JH Duff. Surg. 85: 212-18, 1979.

In 10 fasting dogs receiving 10^9 viable *E. coli* bacteria per kilogram intravenously, mean systolic blood pressure decreased from 120.6 ± 12.8 mmHg. The association of hypoglycemia and increased arterial alanine and glycine wth elevated plasma glucagon implied impaired gluconeogenesis. A rapid elevation of blood urea concentration, indicating increased

ureagenesis, a fall of blood glucose, and an increase of net urea synthesis relative to that of glucose suggested than an increased proportion of the carbon residues derived from glucogenic amino acids is catabolized via pathways other than gluconeogenesis. In the bacteremic dogs the absolute net release from the leg of valine, isoleucine, and leucine and their net release relative to the net rate of proteolysis were decreased, suggesting increased oxidation of these amino acids in skeletal muscle. An increased net release of alanine relative to the net rate of protein catabolism in muscle was in agreement with this contention.

79. *E. coli* Endotoxin Shock in the Baboon: Treatment with Lidocaine or Indomethacin. JR Fletcher, and PW Ramwell. Adv. Prostagland. Thrombox. Res. 3: 183-92, 1978.

The results of this study indicate that lidocaine and/or indomethacin may be useful in treating endotoxin shock in humans. We employed lidocaine or indomethacin prophylactically for endotoxin shock in the baboon. For these drugs to be used in human endotoxin shock, additional experiments, in which treatment is instituted after shock has occurred, should be done.

80. Indomethacin Improves Survival After Endotoxin in Baboons. JR Fletcher, PW Ramwell. Advances in Prostaglandin and Thromboxane Research 7: 821-828, 1980.

It is now well established that the prostaglandins participate in pathophysiological processes such as inflammation (2), thermal injuries (26), hypertension (9), peptic ulcer disease (29), diarrhea (18), dermatological conditions (26), ductous arteriosus constriction (4), abnormalities of platelet function (25), dysmenorrhea (3), fever (21), and shock (5).

Although the exact mechanism by which indomethacin exerts its beneficial effects in these studies is unknown, it is clear that survival is improved, even when treatment is instituted after shock has occurred. The results of this study indicate that indomethacin may be useful in the treatment of shocklike states in humans. We have employed indomethacin in an endotoxin model to help differentiate mechanisms that are contributory to the irreversibility of shock. Additional experiments in a septic shock model are indicated.

81. The Pathophysiology of Shock. RF Wilson. Intens. Care Med. 6: 89-100, 1980.

This is a very brief, superficial and biased discussion of the pathophysiologic changes in shock. It was designed to provide some insight into the very complex changes that occur, with particular attention to a few examples of the impaired cell metabolism, including changes in ATP, cAMP, and calcium. Although inadequate tissue perfusion through nutrient capillaries is the main etiologic factor in most types of shock, it is not the primary problem in many patients, particularly those with early or hyperdynamic sepsis. The importance of oxygen consumption and the possible benefits of higher hemoglobin levels are discussed to some extent because of their possible clinical application.

82. The systemic septic response: does the organism matter? JB Wiles, FB Cerra, JH Siegel, and JR Border. Crit. Care Med. 8: 55-60, 1980.

The clinical and physiological responses to septicemia were evaluated in 59 patients with 70 septic episodes. All patients were critically ill, had similar ICU support, and had positive blood cultures as well as a clinical infection when studied by dye dilution cardiac outputs.

The overall ratio of gram-negative to gram-positive sepsis was 2.6:1.0. Patients with septicemia caused by gram-positive organisms, gram-negative organisms, anaerobes, and fungi had similar fever, leucocyte, and acid base responses. There were also no statistical differences in any physiological variables between organism group or between specific organisms. After volume loading, all patients exhibited a hyperdynamic cardiovascular response with abnormal vascular tone. Some degree of myocardial depression was a common feature of all forms of bacterial or fungal septicemia. Heart rate was the cardiac variable producing the increased cardiac output in this setting.

The exact pathogenesis of the septic response remains undetermined. However, the response appears to be host determined and not peculiar to a specific pathogenic microorganism.

83. Netilmicin: A Review of Toxicity in Laboratory Animals. FC Luft. J. Int. Med. Res. 6: 286-299, 1978.

The data on the toxicity of netilmicin in laboratory animals as well as preliminary data in man are reviewed. Netilmicin is less toxic to the VIIth nerve than is gentamicin in all species tested. The data suggest that is probably is less ototoxic than tobramycin, although confirmatory studies should be performed. Netilmicin is also less nephrotoxic than gentamicin in all species tested. It is less nephrotoxic than tobramycin in the rat and dog. Comparisons in the rat suggest that netilmicin has a flat dose-response curve that resembles the curve produced by streptomycin. In animals, netilmicin produces more neuromuscular blockade than gentamicin; however, neuromuscular blockade with aminoglycosides in man is rare and thus far no episodes have been associated with netilmicin during clinical investigation. Initial clinical studies in man indicate that netilmicin is efficacious and well tolerated. Presently available data suggest that netilmicin offers distinct advantages over older aminoglycosides. Final conclusions must await prospective randomized double-blind trials in man.

84. Gentamicin: toxicity in perspective. WL Hewitt. Postgrad. Med. 50: 55-59, 1974.

A review of published and personal experience with gentamicin in relation to toxicity is presented. Ototoxicity is believed to be extremely uncommon. A gradual rise in serum creatinine is seen in 5-10% of patients and is reversible when the drug is discontinued. Acute renal failure is less frequent and appears to have a multi-factorial pathogenesis.

The adverse effects associated with gentamicin can be categorized into three areas in increasing order of clinical importance-a miscellaneous group, ototoxicity, and nephrotoxicity.

85. Comparative Toxicity of Netilmicin and Gentamicin in Squirrel Monkeys (*Saimiri sciureus*). M Igarashi, JK Levy, and J Jerger. J. Infect. Dis. 137: 476-480, 1978.

Netilmicin was found to be less toxic than gentamicin when administered at comparable dosage levels to squirrel monkeys (*Saimiri sciureus*). This finding is based upon data obtained from the following determinations: length of survival period; change in body weight; observation of general change in behavior after daily injection; ataxia, as measured by the squirrel monkey platform-runway test; acoustic reflex threshold; levels of blood urea nitrogen and serum creatinine (and pathology of the kidney); and microbiological antibiotic assay.

86. Natural history of aminoglycoside nephrotoxicity in the dog. RE Cronin, RE Bulger, P Southern, and WL Henrich. J. Lab. Clin. Med., March 463-474, 1980.

The natural history of aminoglycoside nephrotoxicity is not well described. This study investigated in the dog renal functional and electrolyte abnormalities during and for 20 days following a 10-day course of low-dose gentamicin (7 mg/kg/day), high-dose gentamicin (30 mg/kg/day), and netilmicin (30 mg/kg/day). Renal histology was examined at the end of the study. Renal functional abnormalities occurred only in animals receiving high-dose gentamicin. A fall in maximal urinary osmolality (1579 ± 347 mOsm/kg/H_2O to 450 ± 118, $p < 0.05$) was followed by renal glycosuria and a fall in GFR (66.9 ± 11.9 ml/min to 21.3 ± 8.6, $p < 0.05$). These three functional indices had recovered by day 30 in the survivors. Plasma potassium fell in animals receiving high-dose gentamicin (3.8 ± 0.02 mEq/L to 3.3 ± 0.4, $p < 0.05$) and reached the lowest values (2.7 and 2.9 mEq/L) just prior to death in two animals dying in uremia. Netilmicin also casued a significant fall in plasma potassium (4.3 ± 0.1 mEq/L to 3.9 ± 0.1, $p < 0.05$). Hypocalcemia (10.0 ± 1.3 mg/dl to 7.8 ± 1.4, $p < 0.05$) but not hypomagnesemia developed following high-dose gentamicin. Peak serum aminoglycoside levels after high-dose gentamicin and netilmicin were comparable, but trough levels rose only in high-dose gentamicin animals and paralleled the fall in GFR. Light microscropy of the kidney 3 weeks after high-dose gentamicin demonstrated no proximal tubular necrosis but extensive focal tubulointerstitial nephritis, especially in the juxtamedullary cortex. Similar but less extensive derangements were noted in animals receiving low-dose gentamicin, despite the absence of functional abnormalities. Minor histological abnormalities were noted in animals receiving netilmicin. To summarize: 1) major renal functional and electrolyte abnormalities developed only following high-dose gentamicin and included impaired urinary concentration, glycosuria, reduced GFR, hypokalemia, and hypocalcemia (except for a fall in plasma potassium, similar doses of netilmicin were not nephrotoxic); 2) tubulointerstitial nephritis, particularly in the juxtamedullary cortex, occurred with low-dose gentamicin as well as high-dose gentamicin and may be a factor in delayed or imcomplete recovery form gentamicin nephrotoxicity; 3) in this model, netilmicin at comparable doses was substantially less nephrotoxic than gentamicin; 4) renal potassium wasting may be a hereto fore unrecognized consequence of aminoglycoside administration.

87. Nephrotoxicity of Gentamicin and Tobramycin Given Once Daily of Continuously in Dogs. N. Reimer, D. Bloxham, and W. Thompson. Antimicrob. Chemother. 4: 85-101, 1978.

Forty female mongrel dogs were allocated randomly to treatment with gentamicin or tobramycin, 45 mg/kg/day, by continuous intravenous infusion or once daily intravenous injection for 10 days. Serum aminoglycoside clearness were measured daily and compared on the first and tenth days with urine clearances of exogenous creatinine and aminoglycoside. On the first day of therapy mean serum aminoglycoside concentrations averaged 9.3 mg/l and all three clearances averaged 3.9 mg/kg/min. During the 10 days of therapy these three clearances decreased an average of 48%, but nephrotoxicity was much greater in dogs given continuous intravenous infusions and in those given gentamicin. On the tenth day tissue concentrations of gentamicin in the outer renal cortex averaged 1877 ug g and were greater than renal cortical concentrations of tobramycin that averaged 994 ug g. Tissue aminoglycoside concentrations were equal in dogs receiving once daily of continuous therapy. Despite causing momentary peak serum concentrations of aminoglycosides of 200 to 500 mg/l, once daily intravenous injection was significantly less nephrotoxic than continuous intravenous infusion, and tobramycin was less nephrotoxic than gentamicin in equivalent doses.

88. Comparative Nephrotoxicity of Aminoglycoside Antibiotics in Rats. F. Luft, R. Bloch, R. Sloan, M. Yum, R. Costello, and D. Maxwell. Infect. Dis. 138; 541-545, 1978.

Netilmicin, gentamicin, tobramycin, amikacin, kanamycin, streptomycin, and sisomicin were given daily for 15 days to groups of rats at three dosage levels corresponding to 10, 15, or 25 times the dose recommended for humans on a weight basis. Decreased urinary osmolality and increased urinary excretion of protein and B-N-acetyl hexosaminidase were dose-realted features of nephrotoxicity. Decreased tubular resorption of glucose and phosphate were observed with the most toxic regimens after extensive renal damage had occurred. All aminoglycosided accumulated in renal tissue; however, the concentration of drug in the renal cortex at the time the rats were killed was not useful for the prediction of renal impairment. Streptomycin and netilmicin exhibited a flat dose-response curve with respect to histological damage, as compared with the curves for the other drugs. Results of studies of creatinine clearance and examination of renal tissue suggested the following order of increasing toxicity of the treatment regimens: (1) 0.9% NaCl and uninjected controls; (2) streptomycin; (3) netilmicin; (4) tobramycin; (5) sisomicin, amikacin, and kanamycin; and (6) gentamicin.

89. Comparative Nephrotoxicity of Gentamicin and Tobramycin in Rats. D. Gilbert, C. Plamp, P. Starr, W. Bennett, D. Houghton, and G. Porter. Antimicrob. Agents and Chemotherap. 13: 34-40, 1978.

A rat model was utilized to compare the nephrotoxic potential of gentamicin and tobramycin. Gentamicin, 40 mg/kg per day, predictably produced renal failure and morphological evidence of proximal tubular necrosis over 14 days of treatment. An identical dosage of tobramycin was associated with only minimal morphological changes and normal concentrations of serum creatinine and blood urea nitrogen. Similar results were obtained even after the tobramycin dosage was tripled to 120 mg/kg per day. A decrease in urine osmolality, mechanism unknown, was observed in all gentamicin-treated rats. According to both histological criteria and renal function measurements, gentamicin was more nephrotoxic than tobramycin in this animal model.

90. Nephrotoxicity of Gentamicin. J. Kosek, R. Mazze, and M. Cousins. Lab. Invest. 30: 48-57, 1974.

Administration of gentamicin to healthy Fischer 344 rats regularly and rapidly produced characteristic dose-related functional and anatomical renal changes. Doses as low as 1 mg. per kg. per day resulted in formation of numerous lysosomal cytosegresomes (autographic vacuoles), many of which contained prominent myeloid bodies. They occurred most commonly in proximal convoluted tubular cells, and, to a lesser extent, in glomerular and distal tubular epitheluim. At 10 mg. per kg. per day the above changes were seen together with focal tubular necrosis. Physiologic changes at the 10 mg. per kg. per day dosage were typified by polyuria with decreased urine osmolality. At higher dosages (20 mg. per kg.per day), focal but often very extensive tubular necrosis was associated with large accumulations of myeloid bodies, both within tubular lining cells and in tubular lumina. Functional impairment consisted of polyuria, increased blood urea nitrogen, and decreased urea clearance. Massive tubular necrosis, oliguria, and death in uremia occurred at the 40 mg. per kg. per day dosage.

The findings indicate that gentamicin produces dose-related renal injury even when given to healthy animals in doses comparable to those used therapeutically in humans. Prominent myeloid bodies in lysosomal cytosegresomes of renal tubular epithelium appear to be a sensitive indicator of gentamicin toxicity.

91. Gentamicin in 1978. G. Appel, and H. Neu. Anns. Int. Med. 89: 528-538, 1978.

For a decade gentamicin has been used extensively because of its antimicrobial efficacy and the relatively low prevalence of clinical toxicity. Recently the more frequent appearance of resistant organisms, reports of increased nephrotoxicity and ototoxicity, and the development of newer aminoglycoside antibiotics have raised doubts about the continued use of this agent. This paper reassesses the role of gentamicin. It is clear that an appreciation of the pharmacokinetics and the clinical use of gentamicin as well as an understanding of the patterns of toxicity in animals and humans can lead to more efficient treatment with this antimicrobial agent. Despite ample competition form a number of newer aminoglycoside antibiotics, gentamicin will probably continue to be used widely in the near future.

92. Quantitative Nephrotoxicity of Gentamicin in Nontoxic Doses. B. Trollfors, K. Alestig, I. Krantz, and R. Norrby. Infect. Dis. 141: 306-309, 1980.

The effect of gentamicin on the renal function of 36 patients was studied by means of several techniques. After normal or even subnormal doses of gentamicin, progressively decreasing rates of glomerular filtration, as measured by clearance of (^{51}Cr) ethylenediaminetetracetic acid, were observed in a majority of the patients, although trough and peak concentrations in serum were well below accepted levels of gentamicin tended to increase during the courses of treatment. Changes in levels of serum creatinine were not pronounced enough to demonstrate the decreasing rates of glomerular filtration. Studies on serum and urinary levels of a low-molecular-weight protein, B_2-microglobulin, indicated that gentamicin affects the kidney both on the glomerular and the tubular level. The results emphasized the need for monitoring of gentamicin dosages as well as the need for alternative antibiotics to treat patients with preexisting renal impairment.

93. Intraaortic Balloon Counterpulsation With and Without Reperfusion for Myocardial Infarction Shock. M. DeWood, R. Notske, G. Hensley, J. Shields, W. O'Grady, J. Spores, M. Goldman, and J. Ganji. Circ. 61: 1105-1112, 1980.

Forty patients were treated for cardiogenic shock secondary to acute myocardial infarction. Twenty-one (group 1) were treated with intraaortic balloon counterpulsation and 19 (group 2) were treated with counterpulsation and coronary artery bypass grafting. The groups were similar in age, incidence of previous infarction, initial hemodynamics and coronary anatomy.

The in-hospital mortality between group 1 (52.4%) and group 2 (42.1%) was not significantly different. The difference in long-term mortality between group 1 and group 2 was substantially different (71.4% vs 47.3%). The subset of group 2 (n=12) that underwent reperfusion and counterpulsation within 16 hours from the onset of symptoms of infarction had a lower mortality (25.0%) that the subset (n=7) that underwent operation more than 18 hours after the onset of symptoms (71.4%). The long-term mortality in the subset of group 2 patients operated on within 16 hours after the onset of infarction was significantly different from that in group 1 (25.0% vs 71.4%, $p<0.03$). The data suggest that reperfusion with counterpulsation is more effective when carried out early. Patients who develop shock more than 18 hours after the onset of symptoms of infarction appear to benefit most if treated with counterpulsation alone.

94. Thromboxane Release During Pacing-induced Angina Pectoris: Possible Vasoconstrictor Influence on the Coronary Vasculature. R. Lewy, L. Wiener, P. Walinsky, A. Lefer, M. Silver, and J. Smith. Circ. 61: 1165-1171, 1980.

We developed a radioimmunoassay for plasma thromboxane B_2, the metabolite of the coronary vasoconstrictor thromboxane A_2. To see if thromboxane A_2 is produced during myocardial ischemia, we used atrial pacing to study 14 patients with greater than 75% occlusive coronary artery disease proved by arteriography. Paired samples were taken from the coronary sinus (CS) and an artery (A) for lactate and thromboxane B_2 analysis before pacing. During and after pacing at 140 beats/min, sampling was repeated. Before, during, immediately after and 10 minutes after pacing, percent myocardial lactate extractions (A-CS/A x 100) were 29.3 ± 3.7%, -21.1 ± 12.8%, -74.3 ± 20.3% and 25.1 ± 3.5%, respectively (all changes $p<0.01$). Before pacing, five patients had detectable coronary sinus or arterial thromboxane levels. During pacing, 18% and 40% increased occurred in coronary sinus and arterial blood, respectively (0.8 ± 0.1 to 0.9 ± 0.2 pmol/ml, and 0.5 ± 0.2 to 0.7 ± 0.2 pmol/ml). Immediately after pacing, increases of 204% and 132% occurred in the coronary sinus and arterial blood ($p<0.05$), respectively (2.3 ± 0.9 pmol/ml and 1.2 ± 0.4 pmol/ml. Ten minutes after pacing, thromboxane B_2 returned to prepacing levels. These data indicate that thromboxane A_2 is produced during pacing induced myocardial ischemia and could alter regional coronary blood flow.

95. Prostaglandins and Cardiovascular Function: Some Biochemical and Physiological Aspects. A. Wennmalm. Scand. J. Clin. Lab. Invest. 39: 399-405, 1979.

More than 40 years ago the biological activity of secretions of human accessory genital glands was observed independently by Euler (8) and Goldblatt (9). Euler concluded that the active principle was a pipid soluble acid, and suggested prostaglanding (PG) as a suitable name. This name has been retained ever since, although later studies by Euler showed that the main source of PG in the male genital tract is not the prostate gland but rather the seminal vesicles. PG attracted little interest in laboratories until the late 1950s, when Bergstrom and co workers at the Karolinska Institute isolated several different PGs from the sheep seminal vesicles and elucidated their chemical structures (4,5). Since then, research in PGs has increased tremendously; this year more than 2000 papers will be published in the field.

From the first observation of the blood-pressure decreasing effect of PGs (8) to today's discussion of prostacyclin as a physiological vasoregulator, a considerable number of papers have reported on various possible physiological roles for PGs in the circulatory system. The purpose of the current paper is briefly to describe some of these data, expecially those dealing with PGs in the normal, healthy individual.

96. Temperature: A Critical Factor Determining Localization and Natural History of Infectious, Metabolic, and Immunological Diseases. D. Rodbard, H. Wachslicht, and S. Rodbard. Perspect. Biol. Med. 23: 439-474, 1980.

Enormous attention has been given to the characteristic fevers which occur in the course of infectious diseases (1,pp. 46,52,70,2). Relatively little attention has been given to the effects of regional body temperature differentials on disease processes (3). The human body is not a uniform incubator at 37°C. Instead, there are significant temperature gradients from trunk to extremities (4, pp. 102-105; 5), from hand to fingertips (6), within the external ear (7), anterior chamber fo the eye (8), or wherever two veins happen to cross (9) (figs. 1-4). This temperature profile depends on geographic location, climate, season, humidity, activity, clothing, levels of thyroid hormones, glucocorticoid and sex steriods, and time of day (10,pp. 160,161). In many tropical regions, the skin temperature gradients are relatively constant year-round, possibly contributing to susceptibility to several chronic infections which might be eradicted or supposed by the wider temperature swings in the temperate zones (10,11).

We shall briefly review some of the evidence in support of the hypothesis: Body temperature is a critical factor determining host susceptibility, location of lesions, and the natural history of disease. This principle has been previously enunciated for individual diseases-for example, pneumonia (12), other bacterial

and mycobacterial diseases (13-17), fungal diseases (18), viral diseases (19, pp. 532,598,706; 20,pp. 74,131,144,158,231,325, 350; 21), and protozoal diseases (22-26). However, the enormous generality of this principle in clinical medicine (table 1) has not been fully appreciated or exploited (3). This thesis has numerous corollaries with regard to pathogenesis, diagnosis, treatment, and epidemiology of infectious, metabolic, immunological, and neoplastic diseases.

97. Influence of Endogenous Opiates on Anterior Pituitary Function. D. Van Vugt, and J. Meites. Fed. Proc. 39: 2553-2560, 1980.

In general, the endogenous opioid peptides (EOP), morphine (MOR), and related drugs exert similar effects on acute release of pituitary hormones. Thus administration of opiates produces a rapid increase in release of prolactin (PRL), growth hormone (GH), adrenocorticotropin (ACTH), and antidiuretic hormone (ADH), and a decrease in release of gonadotropins and thyrotropin (TSH). Although not yet fully established, there is growing evidence that the EOP participate in the physiological regulation of pituitary hormone secretion. Thus naloxone (NAL), a specific opiate antagonist, has been shown to reduce basal serum levels of PRL and GH, and to elevate serum levels of LH and follicle stimulating hormone in male rats. Other reports have shown that NAL can inhibit the stress-induced rise in serum PRL, raise the castration-induced increase in serum LH to greater than normal castrate values, and counteract the inhibitory effects of estrogen and testosterone on LH secretion. Opiates appear to have no direct action on the pituitary, but there is evidence that they can alter activity of hypothalamic dopamine and serotonin in modulating secretion of pituitary hormones.

98. Shock Kidney. A. Bohle, S. Mackensen-Haen, K. Grund, H. Christ, E. Krόpfle, and S. Schellhorn. Path. Res. Pract. 165: 212-226, 1979.

A comparison of morphometric studies on autopsy kidneys and biopsies of kidneys from patients with acute renal failure (ARF) showed the following:
Kidneys from patients who developed ARF a few days or weeks before death, are larger at post-mortem examination than kidneys from patients with normal renal function at death, because of an increased fluid content.
In most cases the lumina of the proximal tubules are widened, with the relative epithelial area of the proximal tubules being statistically significantly smaller.
Kidneys with normal function at death show a narrowing of the proximal tubular lumen at autopsy. The epithelial area of the proximal tubules is statistically significantly larger than that of biopsy kidneys with normal function.
We conclude that in kidneys with normal function at death and in those that developed ARF before death, different structural changes appear which must be taken into account when correlating structure

99. Thromboxane A2 in Blood Vessel Walls and its Physiological Significance: Relevance to Thrombosis and Hypertension. AI Ally and DF Horrobin. Prostaglandins and Med. 4: 431-438, 1980.

It has been thought that blood vessels apart from the umbilical artery produce little or no thromboxan (TX) A2. However selective inhibitors of TXA2 biosynthesis have substantial effects on vessel physiology, suggesting that small amounts of TXA2 may be important in regulating function. This indirect evidnece is now supported by direct measurements of TXB2 (the produce of TXA2 conversion) using both gas chromatography-mass spectrometry (GCMS) and radioimmunoassays. At least four independent laboratories have now dmeonstrated TXB2 production by various blood vessels. These studies suggest that vessel wall TXA2 is present in amounts more than adequate to exert biological actions on both vascular reactivity and on platelets. This may require re evaluation and revision of present concepts of hypertension adn thrombosis.

100. The Differential Inhibition of Prostaglandin Synthesis in Platelets and Vascular Tissue in Response to Aspirin. F Shaikh, S Bott, and L Demers. Postagland. Med. 4: 439-447, 1980.

Since aspirin inhibits the platelet as well as vascular prostaglandin synthesis it may therefore, paradoxically induce a thrombotic tendency when used as an antithromboitc agent. The in vivo effect of therapeutic doses of aspirin on the prostaglandin synthetic capacity of the rat platelets and vascular tissue was therefore studied to determine the significance of this paradoxical aspirin effect. A single aspirin dose of 5 mg/kg or greater was found to significantly decrease the synthesis of prostaglandin F by rat platelets. Even the normal augmentation of PGF synthesis by N ethyl maleimide was significantly reduced by this single aspirin dose. In contrast, doses as high as 20 mg/kg of aspirin failed to reduce the production of 6-keto PGF$_{1\alpha}$ by aortic slices from rats pretreated with aspirin. These results indicate that the cyclooxygenase enzyme (CO) system in the prostaglandin biosynthetic pathway within blood vessel walls has the capacity to recovery from the inhibitory effect of aspirin or it is less susceptible to inhibition than the CO in platelets. This relative resistance of CO to the inhibitory effects of aspirin may serve to protect the organism from excessive thrombotic tendencies brought about by the effect of aspirin on the vascular prostaglandin generating system. These results indicate that an aspirin dose of 5-10 mg/kg would be optimal if aspirin were to be used as an antithrombotic agent.

101. Direct Measurement of Leukocyte Motility: Effects of pH and Temperature. C Nahas, M Zamboni, and J Lennon. Proc. Soc. Exp Biol Med. 138: 550-552, 1971.

Rate of locomotion of human PMN is markedly enhanced by temperature between 32° and 42° (x10^{-5} cm/s). The rate is not significantly altered between pH 7.5 and 7.7. Beyond 7.7 there is a significant and rapid inhibition of motility.

102. Pulmonary Hypertension in Sepsis. W. Sibbald, N. Paterson, R. Holliday, R. Anderson, T. Lobb, and J. Duff. Chest 73: 583-591, 1978.

To examine the relative roles of passive factors (flow; filling pressures of left side of heart) and active factors (acidosis; arterial unsaturation) in the genesis of pulmonary hypertension when associated with sepsis, 37 patients with sepsis and 24 patients without sepsis were examined. Pulmonary arterial diastolic-pulmonary wedge pressure gradient (PAd-PWP gradient) and correlated reasonably with a standard formula for calculated resistance ([PA - PWP]/CI, where PA is mean pulmonary artery pressure and CI is cardiac index). In 22 of 37 patients, sepsis was associated with a significant degree of resistance to flow in the pulmonary circulation, as measured by the PAd-PWP gradient; and the higher PAd-PWP gradient, the greater the likelihood of early death. Non of the examined passive or active factors appeared to be adequate to explain pulmonary hypertension when present. By the use of previously derived formulae to estimate the compliance of the elastic pulmonary arteries, factors affecting this part of the pulmonary microcirulation could not be held accountable for apparent pulmonary hypertension. Therefore, the presence of pulmonary hypertension in sepsis appears to be an active, rather than a passive, phenomenon and unrelated to arterial oxygen saturation or acid-base imbalance. Although the exact cause is unknown, pulmonary hypertension in sepsis is associated with a high mortality and may be clinically followed by measurement of the PAd-PWP gradient.

103. Effect of Glucagon on Gastrointestinal Blood Flow of Dogs in Hypovolemic Shock. J. Bond, and M. Levitt. Am. J. Physiol. 238: 434-439, 1980.

A microsphere technique was used to study the effect of glucagon on blood flow to the different tissue layers of the stomach, small bowel, and colon of the dog in hypovolemic shock. In normal dogs, glucagon caused a twofold rise in flow to all layers of the stomach and colon, and a threefold increase to all layers of the small bowel. After administration of glucagon, a larger fraction of cardiac output was diverted to the gut microcirculation. In acute hypovolemic shock, intestinal perfusion was preserved relative to cardiac output inasmuch as cardiac output and gastric blood flow fell 75% and flow to the small bowel and colon fell by only about 50%. Glucagon markedly increased the fraction of cardiac output passing to the gut circulation in hypovolemic shock and, most importantly, sustained flow to the areas most prone to ischemic necrosis: gastric mucosa, colonic mucosa, and small intestinal villi. In more prolonged shock, however, glucagon precipitated fatal cardiovascular collapse unless part of the lost blood volume first was replaced. Glucagon, therefore, should not be used in patients in hypovolemic shock without prior replacement of at least part of the lost blood volume.

104. Gentamicin Nephrotoxicity in the Dog: Sequential Light and Electron Microscopy. W. Spangler, R. Adelman, G. Conzelman Jr., G. Tsuzaki. Vet. Path. 17: 206-217, 1980.

Sequential percutaneous renal biopsies in six dogs given gentamicin at 10 mg/kg every 8 hours (intramuscular) were examined before treatment and 5,9 and 12 days after treatment. Renal function tests (blood urea nitrogen and serum creatinine) and urinary enzyme excretion (β glucuronidase, N acetyl-glucosaminidase, galactosidase and muramidase) were measured daily. Periodic acid Schiff (PAS)-stained, 3-μm sections of renal biopsies taken before drug treatment showed pale and swollen proximal tubular epithelium that occluded the tubular lumen. The apical surface of all proximal tubules (brush border) stained intensely. On day 5, brush border staining was decreased or absent and many proximal tubules had open lumina and hyaline globules in the cytoplasm. Ultrastructurally, the numbers of cytoplasmic lysosomes were increased and most contained large lamellar inclusions (myelin figures). Biopsies on day 9 were characterized by an increase in the size and number of cytoplasmic hyaline globules and an absence of brush border staining. Scattered proximal tubule cells were necrotic. Intact proximal tubules and other parts of the nephron frequently contained amorphous granular casts or necrotic debris. Ultrastructurally, proximal tubules had intact brush borders and showed a remarkable increase in the number and size of lysosomes of all types. On day 12 the severity of these changes progressed, and cytosegrosomes became numerous. Urinary enzyme levels (β glucuronidase and N acetyl-glucosaminidase) were elevated by day 2, galactosidase elevated by day 4 and muramidase elevated by day 5. Clinically significant elevations in serum creatinine (day 6) and blood urea nitrogen (day 12) were preceded by elevations in urinary enzyme excretion and by severe alterations in renal tubular morphology.

105. The Effect of Escherichia Coli Endotoxins and Adrenocortical Hormones on Plasma Enzyme Activities in the Domestic Fowl. M. Curtis, H. Jenkins, and E. Butler. Res. in Vet. Sci. 28: 44-50, 1980.

The intravenous injection of endotoxins isolated from Escherichia coli serogroups 0111 and 078 (2 mg/kg) increased the activities of aspartate transaminase and lactate and sorbitol dehydrogenases in the plasma of six- to 11-week-old chickens during the next 24 h. These changes were compared with those produced by adrenocorticotrophic hormone and β-methasone and were attributed to tissue damage involving the liver followed by increased enzyme synthesis which may have been induced partly by adrenocortical hormones. Further evidence of liver damage was provided by a fall in the activity of cholinesterase. The alkaline phosphatase activity gave no indication of cholestasis.

106. Reactivity of the Cerebrocortical Vasulature and Energy Metabolism to Direct Cortical Stimulation in Haemorrhagic Shock. E. Dóra, and A. Kovách. Acta Physiol. Acad. Scient. Hung. 54; 347-361, 1979.

Direct electrical stimulation of the cerebral cortex was used to determine the changes of cortical carbohydrate and oxidative metabolism and of vascular reactivity during haemorrhagic shock. The results were as follows.

Electrical stimulation of the brain cortex applied in the control period led to a marked vasodilation and NAD reduction that was preceded in part of the experiments by a transient NADH oxidation. It is suggested that the increase in cortical NADH fluorescence observed during direct stimulation is due to the fact that the rate of cytoplasmic NADH production exceeded the rate of mitochondrial NADH oxidation and of the rate of H^+-transport from the cytoplasm into the mitochondria.

The cerebrocortical vasular and NAD/NADH redox state responses induced by electrical stimulation changed in the early hypovolaemic phase of shock. At this time, electrical stimulation of the brain cortex led to NADH oxidation in the majority of the experiments or in some experiments, the stimulation did not bring about changes in the redox state of the cortex. The total loss of the reactivity to direct stimulation of the cerebrocortical vessels and of energy metabolism preceded the occurrence of cortical ischaemia during the hypovolaemic phase of shock.

Since after reinfusion of the shed blood, redox state and vasculature remained unresponsive to stimultaion even in those experiments in which the cortical ischaemia improved, it is concluded that the carbohydrate and oxidative metabolism of the brain cortex were already irreversibly damaged in the early phase of hypovolaemic shock.

107. Mechanism of Traumatic Shock. R. Hardaway III. Surg. Gynecol. Obstet. 151: 65-69, 1980.

Although many attempts have been made to demonstrate the existence of a shock-producing toxin, little success has been attained. Traumatic shock is generally believed to be caused by simple loss of blood.

Evidence is presented that tissue trauma causes hemolysis. Although hemoglobin is harmless, the stroma of the broken red cells is a clotting stimulant which, in the presence of the slow capillary flow of hemorrhagic shock, sustains a continuing disseminated intravascular coagulation. This disseminated intravascular coagulation produces a clotting defect, morbidity and death. The condition is not responsive to intravenously administered fluids but is responsive to fibrinolysin therapy.

108. Changes of Basic Biochemical Indices in Rat Liver Tissue After Intraperitoneal Application of Endotoxin. B. Hejcmanova, Z. Konickova, J. Musil, and J. Moserova. Acta Chirurg. Plast. 21: 182-190. 1979.

The present spread of gram-negative infection coupled with increased incidence of accompanying shock reactions has recently provoked lively discussion on the role endotoxin has to play in the development of such conditions. Endotoxin is often referred to as the main pathological factor responsible for the development of shock as such. In order to see to what extent a similar mechanism could be presumed in the development of burn and endotoxin shock we decided to compare the changes in basic biochemical indices in the liver tissue of rats after burns (2) with those after the application of endotoxin.

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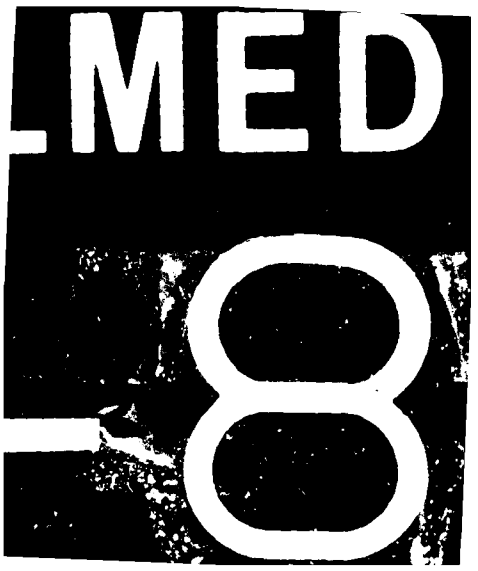
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